

A watercolor illustration of a heart, rendered in soft pink and light blue washes. A vertical surgical incision is shown on the left side of the heart, with three small 'X' marks representing sutures. The background features faint, abstract watercolor splashes in pink and blue.

# TETRALOGY OF FALLOT IN FINLAND

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# **TETRALOGY OF FALLOT IN FINLAND**

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*To Elina, Tyyne and Saimi*



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# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I                **Need of transannular patch in tetralogy of Fallot surgery carries a higher risk of reoperation but has no impact on late survival: results of Fallot repair in Finland.** Ylitalo P, Nieminen H, Pitkänen OM, Jokinen E, Sairanen H. Eur J Cardiothorac Surg. 2015 Jul; 48(1):91-7
- II                **Late gadolinium enhancement (LGE) progresses with right ventricle volume in children after repair of tetralogy of fallot.** Ylitalo P, Pitkänen OM, Lauerma K, Holmström M, Rahkonen O, Heikinheimo M, Sairanen H, Jokinen E. Int J Cardiol Heart Vessel. 2014 Feb 12; 3:15-2
- III                **Additional mechanism for left ventricular dysfunction: chronic pulmonary regurgitation decreases left ventricular preload in patients with tetralogy of Fallot.** Ylitalo P, Jokinen E, Lauerma K, Holmström M, Pitkänen-Argillander OM. Cardiol Young. 2018 Feb;28(2):208-213
- IV                **Postoperative pulmonary regurgitation in adolescents with tetralogy of Fallot leads to increased longitudinal strain.** Ylitalo P, Lehmonen, L, Lauerma K, Holmström M, Pitkänen-Argillander O, Jokinen E. Submitted 03/2019

The publications are referred to in the text by their roman numerals.

# ABBREVIATIONS

ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
CHD	Congenital Heart Defect
CMR	Cardiac Magnetic Resonance
DORV	Double Outlet Right Ventricle
ECG	Electrocardiogram
EF	Ejection Fraction
FT	Feature Tracking
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVEDV	Left Ventricular End Diastolic Volume
LVESV	Left Ventricular End Systolic Volume
MRI	Magnetic Resonance Imaging
PR	Pulmonary Regurgitation
PVR	Pulmonary Valve Replacement
RV	Right Ventricle
RVEDV	Right Ventricular End Diastolic Volume
RVESV	Right Ventricular End Systolic Volume
RVOT	Right Ventricle Outflow Tract
RVOTO	Right Ventricle Outflow Tract Obstruction
rTOF	repaired Tetralogy of Fallot
SCD	Sudden Cardiac Death
TAP	Transannular Patch
TGA	Transposition of Great Arteries
TOF	Tetralogy of Fallot
TV	Tricuspid Valve
UVH	Univentricular Heart
VSD	Ventricular Septal Defect

# ABSTRACT

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. Postoperative patients with TOF are mostly compromised by chronic pulmonary regurgitation and chronic right ventricular volume load. These patients suffer from impaired exercise capacity and have an increased risk of sudden cardiac death (SCD) and heart failure.

This thesis investigates the long-term outcome of surgically corrected TOF patients in a population-based setting. It also assesses the effects of long-lasting pulmonary regurgitation (PR) in the postoperative state in children and adolescents with TOF and healthy control subjects.

During the period from 1962 to 2007 a total of 600 patients with TOF were surgically corrected in Finland before the age of 15 years. The follow-up time of these patients was  $23 \pm 12.1$  years. We observed that:

- i. 514 (85%) patients were alive and living in Finland; 82 (14%) had died. Primary repair of TOF was found to predict lower mortality and longer event-free survival when compared with two-stage repair. The need for a transannular patch (TAP) in TOF surgery carried a higher risk of re-operation without impact on late survival.

In addition to the population-based follow-up study, we conducted a single-centre cross-sectional study including 45 patients after repair of tetralogy of Fallot (rTOF) and 45 healthy age- and gender-matched paediatric and adolescent volunteers as controls (CO). Cardiac magnetic resonance (CMR) imaging was performed on all the study subjects. We made the following observations:

- ii. Late gadolinium enhancement (LGE), detected with CMR after gadolinium contrast agent, was also found outside the surgically affected areas in the right ventricle (RV) of TOF patients. Severity of PR correlated with the degree of LGE. LGE is recognized as a marker of fibrosis, scars, or otherwise abnormal myocardium.
- iii. In children and adolescents with TOF, severe pulmonary regurgitation importantly affects volume flow through the left atrium. Reduction in left ventricular (LV) preload volume may be an additional factor contributing to LV dysfunction.
- iv. RV longitudinal strain is increased in paediatric TOF patients with severe pulmonary regurgitation. In comparison with healthy volunteers, all TOF patients demonstrated enhanced and delayed RV circumferential strain that was accentuated in the apical region.

In conclusion, the late results of TOF surgery are excellent. Patients operated on in the last two decades can expect to have a life expectancy comparable to their healthy peers. Early primary correction and avoidance of TAP if possible are predictors of superior late outcome.

Chronic pulmonary regurgitation has deleterious effects on both right and LV filling and function. Novel methods such as LGE analysis, feature tracking (FT), and evaluation of LV preload may prove valuable when assessing the need for pulmonary valve replacement (PVR).

## YHTEENVETO SUOMEKSI (FINNISH SUMMARY)

Sydämen rakennevikana on kaikkein yleisin yhteen elimeen kohdistuva rakennevika. Rakenteellinen sydänvika todetaan n. 1 %:lla vastasyntyneistä. Potilaiden ennuste on parantunut huomattavasti viime vuosikymmenien aikana, ja aikuisiän on saavuttanut jo yli 7000 sydänlasta. Hyvästä ennusteesta ovat poikkeuksena kuitenkin syanoottiset sydänviat, joilla tarkoitetaan ryhmää synnynnäisiä sydänvikoja, joissa sydämen oikean ja vasemman puolen välillä on oikovirtaus aiheuttaen verenkierron happivajasta ja sinisyyttä. Kun muiden rakenteellisten sydänvikojen ennuste alkaa lähentyä verrokkiväestöä, oikeaa kammiota kuormittavien syanoottisten sydänvikojen ennuste on edelleenkin merkittävästi verrokkiväestöä huonompi, ja potilailla on normaaliväestöä suurempi riski kuolla joko sydämen vajaatoiminnan tai sydänperäisen äkkikuoleman vuoksi. Yleisyydeltään suurin ja merkittävin syanoottinen sydänvika on Fallot'n tetralogia.

Tutkimuksessa käytettiin koko väestön kattavaa synnynnäisten sydänvikojen rekisteriä, jonka avulla kaikkien Suomessa leikattujen Fallot-potilaiden sairastuvuutta, kuolleisuutta sekä erilaisten kirurgisten menetelmien vaikutusta myöhäistuloksiin voitiin selvittää. Otimme tutkimukseen mukaan kaikki Suomessa alle 15-vuotiaana korjausleikatut Fallot-potilaat, joita oli yhteensä 601. Rekisterin tietoja käyttämällä ja niitä väestörekisteriin ja potilasasiakirjoihin yhdistämällä selvitimme 99,8% kattavuudella potilaiden myöhäistuloksen sekä merkittävältä osalta myös käytetyt kirurgiset menetelmät sekä uusintaleikkausten määrän. Lisäksi tutkimme kliinisessä potilas-verrokkiasetelmassa Fallot-lapsia ja nuoria sekä heidän ikäisiään terveitä verrokkihenkilöitä. Tavoitteena oli selvittää sydämen magneettikuvaksella Fallot-potilaiden sydämen toimintaa ja vajaatoiminnan kehittymislöydöksiä lapsuus- ja nuoruusiässä. Erityisenä mielenkiinnon kohteena oli Fallot-potilaille tyypillisen keuhkovaltimoläpän vuodon merkitys sydämen toiminnan ja rakenteellisten muutosten taustalla. Kliinisessä potilaskohortissamme tutkimme yhteensä neljäkymmentäviisi 7-19-vuotiasta Fallot-potilasta sekä 48 tervettä saman ikäistä verrokkihenkilöä. Tutkimuspotilaat tutkittiin vuosina 2008-2012.

Tutkimuksessa osoitettiin, että Fallot'n tetralogian korjaaminen käyttäen keuhkovaltimoläppärenkaan katkaisevaa ja sitä laajentavaa keinomateriaalipaikkaa aiheuttaa merkittävän keuhkovaltimoläpän vuodon ja kasvattaa merkittävästi potilaan riskiä joutua uusintaleikkaukseen, kun heitä verrattiin potilaisiin, joiden läppärensä voitiin jättää koskematta. Tämä tulos on tärkeä arvioitaessa käytössä olevia kirurgisia menetelmiä ja antoi meille mahdollisuuden arvioida suomalaisen kirurgian myöhäistuloksia eri leikkausmenetelmiin liittyen. Lisäksi selvisi, että primaarikorjaus ilman edeltävää apuleikkausta tuottaa paremman lopputuloksen, sillä potilaiden

kuolleisuus on merkittävästi alhaisempi ja he joutuvat selvästi harvemmin uusintaleikkaukseen kuin potilaat, joille on tehty palliatiivinen toimenpide ennen korjausta. Tämä tulos tukee vallalla olevaa käsitystä siitä, että potilaat tulisi pääosin pyrkiä korjaamaan ilman välivaiheen apuleikkauksia.

Kuvantamistutkimuksessa selvisi, että keuhkojen läpi virtaava verivolyymi on tavallista vähäisempi Fallot-potilailla, mikä johtaa sydämen vasemman eteisen verenvirtauksen pienenemiseen ja alentuneeseen vasemman kammion esikuormaan. Esikuorma oli alentunut merkittävästi enemmän niillä potilailla, joilla oli vaikea keuhkovaltimoläppävuoto. Tällä havaitsemallamme verenkierron poikkeavuudella saattaa olla merkittävä osuus myöhemmin ilmaantuvan vasemman kammion vajaatoiminnan kehittymisessä. Esikuorman arviointi voi mahdollisesti jatkossa olla yksi menetelmä, jolla varhainen kehittyvä vajaatoiminta havaitaan.

Fallot'n tetralogiaa sairastavien potilaiden sydänlihaksen rakenteellisesti poikkeava jo lapsuusiässä. Magneettikuvauksen myöhäistehostumatekniikalla havaittiin, että fibroosiin viittaavia tehostuma-alueita esiintyi oikeassa kammiossa myös kirurgisesti operoitujen alueiden ulkopuolella. Tehostumia oli merkittävästi enemmän keuhkovaltimoläppävuodon vaikeutuessa, oikean kammion laajentuessa sekä leikkauksen jälkeisen seuranta-ajan pidentyessä. Myöhäistehostumien arviointi on mahdollinen tulevaisuuden menetelmä arvioitaessa sydänlihaksen kuntoa ja mahdollista uusintaleikkauksen tarvetta.

Tutkimuksessa huomattiin myös, että magneettikuvauksessa käytettävä feature tracking (FT) strain-analyysi soveltui lapsipotilaiden sydänlihaksen liikehäiriöiden selvittämiseen. Liikelöydökset poikkesivat kaikilla potilailla terveiden verrokkien mittauksiin verrattuna. Keuhkovaltimoläppävuodon huomattiin vähentävän oikean kammion seinämäliikettä kuvaavia strain-arvoja etenkin eteiskammionläppäpäässä, mutta strain-arvot voimistuivat kompensatorisesti kohti sydämen kärkeä. FT-analyysi tarjoaa mahdollisen menetelmän oikean kammion vajaatoiminnan ja liikehäiriöiden varhaiseen tunnistamiseen ja sillä saattaa olla merkitystä arvioitaessa mahdollista uusintaleikkauksen tarvetta ja ajoitusta.

Tutkimustemme mukaan Fallot-potilaiden ennuste parantunut merkittävästi vuosikymmenten aikana. TOF potilaille kannattaa, mikäli vain mahdollista, tehdä varhaislapsuudessa suora kirurginen korjaus ilman edeltävää oireita lievittävää leikkausta. Potilaiden hankalin myöhäisongelma on vaikea keuhkovaltimoläppävuoto, jonka totesimme vähentävän keuhkojen läpi kiertävän veren määrää ja vaikuttavan haitallisesti sydämen vasemman puolen toimintaan. Tämä on uusi havainto. Löysimme Fallot-potilaiden sydäimestä arpeutumiseen viittaavia löydöksiä magneettikuvauksen myöhäistehostuma-tekniikalla ja totesimme löydösten liittyvän seuranta-ajan pituuteen ja keuhkovaltimoläpän vuodon määrään. Magneettikuvauksen strain-analyysillä osoitimme, että TOF-potilaiden sydänlihaksen liikkuvuus on poikkeavaa ja liikehäiriön vaikeusasteella on yhteys keuhkovaltimoläpän vuotoon. Näiden löydösten toivomme tuovan lisäinformaatiota Fallot-potilaiden lääketieteelliseen seurantaan, joko suoraan käytettynä tai osana

tulevaisuudessa mahdollisesti kehitettäviä algoritmejä, jotka hyödyntävät ja analysoivat laaja-alaisesti potilaasta tutkittuja muuttujia. Kummassakin tapauksessa ne voisivat auttaa hoitavia lääkäreitä jatkohoitoon ja uusintaleikkauksiin liittyvässä päätöksenteossa.

# 1 INTRODUCTION

The congenital heart defect TOF is observed in 3% to 6% of every 10 000 births and is the most common cyanotic congenital heart defect. Before the era of corrective surgery, only half of TOF patients survived the first years of life and only a few reached adulthood.

In 1954 Lillehei performed the first intra-cardiac repair of TOF by using cross-circulation. The first patient in Finland was corrected in 1960. Over 700 patients have since been surgically corrected in Finland, and an increasing population of these patients have reached adult age.

Nowadays, during the modern surgical era, most if not all patients survive initial surgery and can expect to have a close to normal exercise capacity in childhood and adolescence. Despite the drastically improved outcome of TOF patients during the recent decades, both internationally and in Finland, these patients still suffer from chronic pulmonary regurgitation. The post-operative course after adolescence is compromised by several complications such as decreased exercise capacity, rhythm disturbances, and even SCD. A re-operation to replace the pulmonary valve is often needed during adolescence or early adulthood. Even though TOF has long been emphasized as a right-sided congenital defect, the role of the left ventricle (LV) as an important determinant of TOF outcome has emerged in recent years. Several chromosomal abnormalities, most commonly trisomy 21 (Down syndrome) and 22q11 microdeletion, are often associated with TOF and compromise the outcomes of this patient group.

In this thesis, we examined the late results and causes of death of TOF patients in Finland. The impact of surgical methods on mortality and morbidity was also assessed in a population-based setting. We aimed to investigate how chronic pulmonary regurgitation, in addition to the RV, also affects LV haemodynamics and myocardial function. We also studied novel clinical and radiological markers of cardiac morphology and function in a prospective patient cohort with healthy controls.



## 2 REVIEW OF THE LITERATURE

### 2.1 HISTORY AND CLINICAL FEATURES

#### 2.1.1 HISTORY

William Harvey introduced the revolutionary concept of two separated circulations (systemic and pulmonary) in 1628(1). This observation served as the basis for the first recognition of tetralogy of Fallot (TOF), which dates back to 1671 in Denmark when Niels Stenson described TOF in a foetus with ectopia cordis(2). It took more than a century before other investigators described similar anatomy(3). An elegant anatomical description was illustrated by William Hunter in London in 1784 in his private publication “Medical observations and inquiries”(4). He stated:

*“...the passage from the right ventricle into the pulmonary artery, which should have admitted a finger, was not so wide as a goose quill; and there was a hole in the partition of the two ventricles, large enough to pass the thumb from one to the other. The greatest part of the blood in the right ventricle was driven with that of the left ventricle into the aorta, or great artery, and so lost all the advantage which it ought to have had from breathing”.*

Hunter described this disease as a combination of three malformations: ventricular septal defect, subpulmonary and pulmonary valve stenosis, and right ventricular (RV) hypertrophy.

Another hallmark description was made by Ethienne-Louis Fallot in 1888 as he proposed that there was a single pathologic foetal process that resulted in association of these different anatomic features (5, 6). However, the term “tetralogy of Fallot” was not used by him as he called this defect “la maladie bleue” or “cyanose cardiaque”. The term tetralogy of Fallot was established by Maude Abbot in Canada in 1924 and the features of this tetrad were coined according to four distinct anatomic features: ventricular septal defect (I) with over-riding of the aorta (II), RV outflow obstruction (III), and RV hypertrophy (IV).

**Figure 1** Etienne-Louis Arthur Fallot (1850-1911)

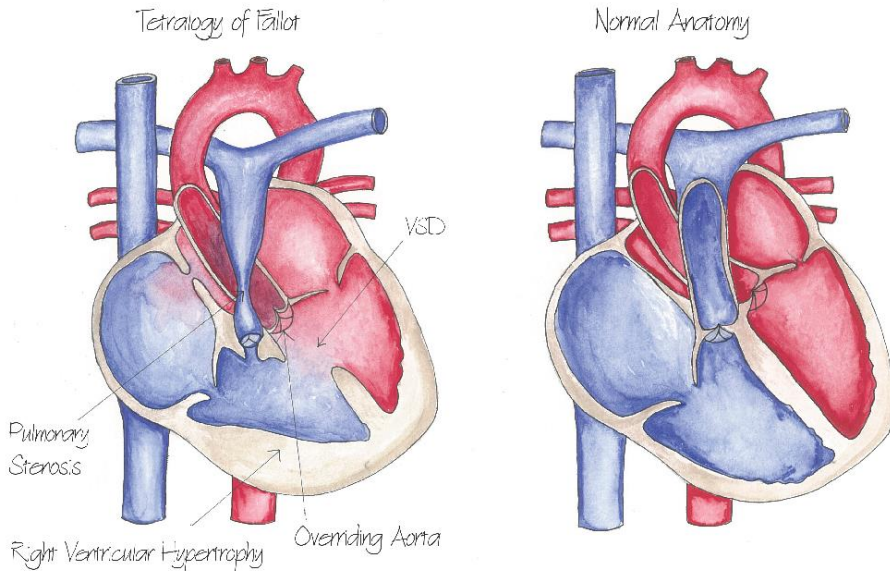


Characteristic to this “anatomic era” of TOF was the continuously expanding comprehension of its anatomic and clinical features. In the early 20<sup>th</sup> century, many new diagnostic tools became available that were successfully incorporated to assist clinical cardiological practice. A remarkable clinical landmark was Maude Abbot’s introduction of circulatory and auscultatory diagrams, the chest x-ray, and findings from a TOF patient’s electrocardiogram in 1936(7).

### **2.1.2 CLINICAL FEATURES**

In the recent literature the anatomic features of TOF have been described as follows: “anterocephalad deviation of the right ventricle outlet septum or its fibrous remnant, combined with a malformed arrangement of the septoparietal trabeculations which produce an annular obstruction at the infundibulum”(8).

**Figure 2** Diagrams of normal heart anatomy and TOF anatomy. Three types of pulmonary stenosis (supravalvar, valvar, and subvalvar) are illustrated. Illustration by Emma Eskola.



It has been suggested that TOF results from underdevelopment of the subpulmonary infundibulum. The spectrum of disease is wide ranging from mild right ventricular outflow tract obstruction (RVOTO) to complete obstruction. When the outflow tract is completely obstructed, the condition can also be called pulmonary atresia with VSD, or “tetralogy of Fallot with pulmonary atresia”. The classic and most common type of TOF can be defined when the heart has normal segmental anatomic structure, the right ventricular outflow tract is patent at birth, and other significant intracardiac abnormalities do not coexist(8). These associated defects could for example be atrial septal defect (ASD) right aortic arch, atrioventricular septal defect (AVSD, mostly associated with Down syndrome), multiple VSDs, double outlet right ventricle (DORV), anomalous left anterior descending coronary artery, and straddling mitral valve (SMV)(9).

### 2.1.3 NATURAL HISTORY

Despite advances in diagnostics and pathological understanding in the early 20<sup>th</sup> century, there were few options to reduce the morbidity in these children, who often died at a young age. In a study on the natural history of TOF published in 1978, 66% of patients born with the defect (including the pulmonary atresia variant) were alive at the age of 1 year. Remarkably, the instantaneous risk of death was highest in the first year of life, slowly decreasing until 10 years of age. At this age, however, the attrition rate remains relatively constant at 6.4% per year **REF12**. Table 1 summarizes the percentages of death at different ages according to the literature.

**Table 1.** *Natural survival of TOF patients [modified from Loh et al., Campbell et al. and Bertranou et al.(10-12)]. Rate of death from birth expressed as percent.*

Age (years)	Percentage of death
1	10-34
3	23-49
5	33
10	55-76
20	84
30	96

When interpreting these results, it must be recognized that the pulmonary atresia variant is an anatomical variant of TOF with especially poor prognosis. When these patients are omitted from survival calculations, still only one third of the patients survive to the age of 10 years(12). The most common causes of death are severe hypoxemic spells (62%), cerebrovascular accidents (17%), and brain abscesses (13%)(10).

### 2.1.4 CLINICAL PRESENTATIONS

The severity of RVOT obstruction mostly dictates the clinical features of TOF after birth. Patent ductus arteriosus and collateral arteries from the systemic to the pulmonary side most commonly modify this picture (13). Table 2 summarizes the different clinical presentations of TOF after birth based on the severity of muscular RVOT obstruction.

**Table 2.** Clinical presentations of TOF at birth (modified from Redington et al.(13))

<b>Clinical features when subpulmonary obstruction is severe</b>
<ul style="list-style-type: none"> <li>•persistent cyanosis apparent within first hours or days of life</li> <li>•cyanosis is provoked when crying, feeding, and doing other activities</li> <li>•metabolic acidosis resulting from arterial desaturation, compensated by increased respiratory rate</li> <li>•in duct-dependent setting, pulmonary flow is derived from left-to-right shunt and from ductus arteriosus and treatment with prostaglandin E is vital</li> <li>•hypercyanotic spells may occur</li> </ul>
<b>Clinical features when subpulmonary obstruction is moderate</b>
<ul style="list-style-type: none"> <li>•acyanotic at birth</li> <li>•systolic murmur usually detected in routine examination</li> <li>•cyanosis develops with increasing infundibular stenosis</li> <li>•cyanosis is noted within the first weeks of life, sometimes delayed</li> <li>•hypercyanotic spells may occur</li> </ul>
<b>Clinical features when subpulmonary obstruction is minimal</b>
<ul style="list-style-type: none"> <li>•mostly acyanotic</li> <li>•feed poorly</li> <li>•gain weight poorly</li> <li>•as right ventricular hypertrophy develops, cyanosis and other typical features are exhibited</li> </ul>

Hypercyanotic spells are an important and often dramatic clinical feature of infants with TOF. These spells refer to sudden profound cyanosis and drowsiness that are sometimes associated with loss of consciousness. These bouts of deterioration can be dangerous and may result in brain injury or even death. Severe spells may last 15 to 60 minutes and are most commonly observed in infants and toddlers from 6 to 24 months of age. Other manifestations, such as convulsions, hyperpnoea, or very fast deep breathing are also possible. Hypercyanotic spells may possibly result from infundibular spasm (14) as a primary cause. Others suggest that these spasms are secondary to systemic vasodilation, reduced RV preload, dehydration, or some other source of sympathetic activity(13). Primary treatment of spells includes oxygen, pacifying the infant in knees-to-chest position with or without

sedation, hydration and increasing peripheral resistance with medication. Hypercyanotic spells may be prevented with the use beta-blockade. Surgical intervention or catheterization should be considered in the tertiary unit. These infants are considered as high-risk patients and surgery (palliative or corrective) is often performed in early infancy(15).

Chromosomal anomalies are frequently diagnosed in TOF patients (25%). The two most common findings are trisomy 21 (Down syndrome) and microdeletion of the q11 region of chromosome 22 (22q11 microdeletion) (16) with a prevalence up to 25%(17).

### **2.1.5 DIAGNOSTICS**

Similar to many cyanotic and other complex congenital heart defects, TOF can be diagnosed during pregnancy in the second trimester morphological ultrasound screening scan. Antenatal detection rates are 13% to 43% (18-20). The foetal diagnosis is especially beneficial for foetuses with severe right ventricular outflow tract obstruction. In these cases, the antenatal diagnosis allows better planning of neonatal care and facilitates sufficiently early prostaglandin treatment for selected patients to avoid spontaneous closure of ductus arteriosus, which therefore prevents possible life-threatening postnatal cyanosis(8). This is particularly important for neonates whose prenatal echo suggests retrograde flow in the ductus arteriosus. Nevertheless, most TOF babies are born without diagnosis and present the condition after birth. It is possible to strongly suspect TOF after comprehensive clinical assessment of the neonate. The typical clinical findings in the newborn with severe TOF are cyanosis and a systolic ejection murmur with a single second heart sound heard on auscultation(13). The diagnosis must be verified by transthoracic cross-sectional echocardiography with a complete description of the cardiac morphology performed in a systematic and sequential protocol. Other pre-operative diagnostics, such as CMR or catheterization, are seldom needed before the primary procedure as ultrasound is sufficient to demonstrate all clinical attributes needed for the TOF diagnosis (8).

## **2.2 SURGERY**

### **2.2.1 SURGICAL HISTORY**

The first steps towards the surgical treatment of TOF were taken at the Johns Hopkins Hospital in the USA in the early 1940s, where Dr Helen Taussig had observed that some children with cyanotic heart defect did better than others as long as their ductus arteriosus remained open but died shortly after the duct closed. Taussig approached cardiac surgeon Alfred Blalock, who created a left subclavian to left pulmonary artery anastomosis in an operation that took less

than 1.5 hours. After performing two other shunt operations, Blalock together with Taussing published this landmark series in 1945. Shunting was a palliative procedure and attempts to relieve the cyanosis but leaves the anatomical defect itself untouched. The repair of intracardiac malformation would need open heart surgery and it took several years before perfusion techniques were sufficiently developed to permit it.

The first intracardiac procedure to correct a congenital heart defect was performed in 1953, when an atrial septal defect was closed through atriotomy by using hypothermia and inflow occlusion(21). Early attempts in performing open heart surgery on cardiopulmonary bypass were discouraging. However, Lillehei and his colleagues performed experiments with dogs using cross-circulation to permit open heart surgery with good outcomes. In 1954 Lillehei used controlled cross-circulation on a boy of 11 years to correct his ventricular septal defect. The boy's father was under anaesthesia and circulated and oxygenated his son's blood (22). In the same year, using this bypass method, he performed the first complete repair on a Fallot patient. In his series using cross-circulation he operated on a total of 49 patients of whom 22 survived(23). Despite this success, cross-circulation was abandoned because of the risks it posed to the donor. Nevertheless, Lillehei proved that by using extracorporeal circulation, open heart surgery was possible and the first successful mechanical cardiopulmonary bypass circuits were soon developed. Of special importance was J.W. Kirklin, who by a heart-lung machine set the standard for extracorporeal circulation and performed over 500 operations of complete repair of TOF as a primary procedure or as secondary to shunt placement (24-27). Despite the success, several complications and technical issues were associated with early surgery of TOF. These included poor systemic perfusion, coronary air embolism, inadequate myocardial protection, and coronary artery injuries(28, 29).

### **2.2.2 TOO EARLY OR TOO LATE?**

During the early days of TOF surgery, complete repair was seldom performed on a patient under 3 to 5 years of age. In fact, an operating age of <5 years was associated with the highest early mortality; the best early survival was observed in age group of 5 to 15 years (30). However, in an early detailed report of infant patients undergoing repair, the authors observed increased mortality if the patient was followed until >2 years of age before complete repair (31). In this important study of Bonchek and Starr, the researchers noted that it was advantageous to perform repair at a younger age and to avoid waiting for the child to grow older. They also suggested that earlier timing would be beneficial in avoiding fibrosis and poor development of the RVOT. They observed that palliative shunting did not improve RVOT development and might even be detrimental and proposed that pulmonary annulus needs sufficient blood flow

for its development to prevent pulmonary atresia. In addition, this study was later recognized as an important description of the natural history of TOF pathophysiology(32). Later, several authors have presented that the repair of TOF can be achieved with good results even in neonates and infants(33-35). Accordingly, despite attempts during the three latest decades to move towards an earlier repair, controversies exist about the correct timing of the primary repair. Presently, it is widely a accepted policy that asymptomatic non ductus-dependent infants should be operated between 6 to 12 months of age. In our tertiary unit in Helsinki University Hospital for Children and Adolescents, we attempt primary repair on most TOF patients before the age of 9 months.

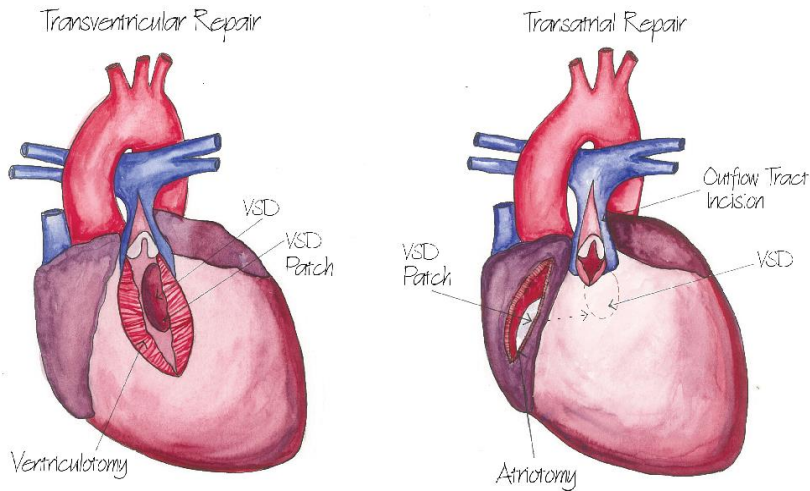
### **2.2.3 SURGICAL TECHNIQUES**

Primary TOF surgery follows either a one-stage or two-stage protocol. One-stage refers to primary intra- and extracardiac repair, while two-stage refers to primary palliation with a shunt followed later by intracardiac repair. The two-stage repair procedure starts with the insertion of a Blalock-Taussig shunt, modified Blalock-Taussig shunt, or other shunt as the primary surgical palliation. The postoperative phase is associated with only partial relief of cyanosis. Palliation is later followed by a repair procedure. Currently, early primary repair is commonly preferred whenever the primary morphology is favourable.

Surgical techniques have developed over decades for the intracardiac procedure. In the early days of surgery, the RV was vented from a large transverse or longitudinal ventriculotomy. Although transatrial-transpulmonary approaches were introduced in the 1960s, they were widely brought to Fallot surgery in the early 1990s to avoid the detrimental ventriculotomy(16). In a traditional approach, the free wall of the RV is vented and both the ventricular septal defect and the obstructed right ventricular outflow tract are accessed through the same incision. In the transatrial approach, VSD is operated via atrial incision through the tricuspid valve and the RVOT obstruction is repaired from a smaller vent to the main pulmonary artery. The ventricular septal defect is closed with a patch and obstructive infundibular muscle fibres are resected. If necessary, the infundibulum or pulmonary annulus is enlarged with a patch to achieve better relief of obstruction(32, 36).

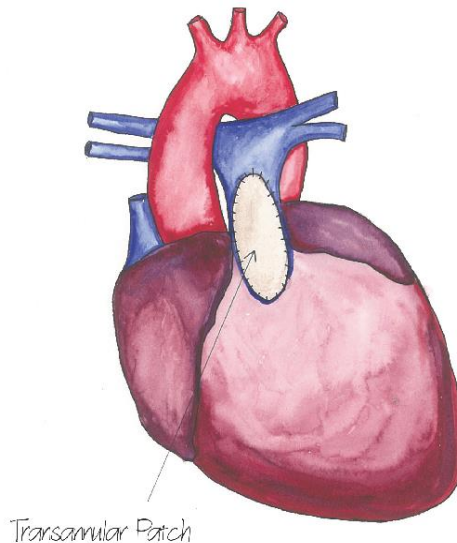


**Figure 3** Transventricular and transatrial surgical techniques. In transventricular repair, both VSD and pulmonary stenosis are operated through a single incision. In transatrial repair, a VSD patch is inserted via atriotomy and pulmonary stenosis is operated through incision of the right ventricular outflow tract. Illustration by Emma Eskola.



An important objective in developing the technique has been to preserve the pulmonary valve (37-39). This approach is currently used in almost all cases of total repair of Fallot irrespective of the primary condition and age of the patient (16, 39, 40). This is because transannular patching has consistently been reported as a significant risk factor for re-operation due to postoperative pulmonary regurgitation (PR) (41). Accordingly, a recent study with 16 years of follow-up showed that patients subjected to TAP exhibit a significantly higher risk of redo procedures but without difference in mortality(42). These observations have been contested by Bacha et al., who reported that the use of a TAP did not reduce late survival and did not increase the risk of a later re-operation (43). Another recent investigation suggested that the use of TAP had no effect on late survival and had a lower incidence of RVOT re-stenosis, probably due to significantly greater relief of RVOT obstruction than in those whose pulmonary annulus was left untouched(44). However, a recent report contested this notion since it demonstrated that the use of TAP was not associated with higher risk of late death, risk of re-operation, or risk of PVR (45). Hickey et al. stated that the annulus-sparing technique reduced the risk of RV dilation significantly in long term(46).

**Figure 4** Transannular patch to relieve right ventricular outflow tract obstruction.  
Illustration by Emma Eskola.



Simultaneous tricuspid valve repair has been under active research during the contemporary era of repair for cases where PR is associated with severe tricuspid valve regurgitation. The results are somewhat controversial and there is no current consensus (47-50). On one hand, PVR by itself seems to improve TR, thus making TV repair unnecessary. On the other hand, it is possible that in the presence of the most severe degrees of TR the pathological changes of TV are irreversible(51).

When interpreting these somewhat controversial results, it is worth noting that the indications and timing of redo procedures differ between institutions, which has an impact on the incidence of operations. The choice of surgical technique is affected by the original morphology and patients with a severe defect are likely to undergo initial palliation or a more comprehensive surgery including a transannular procedure. Because of this, it is difficult to precisely distinguish whether the higher re-operation rate of TAP patients is because of surgical technique or the severity of the primary condition.

Two-stage repair is associated with a myriad of untoward sequelae including the fact that it only partially relieves cyanosis, induces longer-lasting RV pressure loading, promotes distortion of the branch pulmonary arteries,

and is associated with death(43, 52). This approach is thus often avoided. With symptomatic infants some authors suggest that these patients should undergo two-stage repair(32) but other reports suggest that both approaches are reasonable choices as they have similar overall outcomes(53). The arguments for the two-stage strategy are the greater possibility to avoid TAP in the youngest patients and its influence on late outcome. The shunt can also facilitate growth of the pulmonary valve and pulmonary branches and small infants can avoid bypass and circulatory arrest procedures. Authors supporting early primary repair base their opinion on the normalization of growth and development of the heart and circulatory systems, and that by primary repair infants avoid long-lasting hypoxaemia and the adverse effects of hypercyanotic spells(43, 52). Finally, a long-lasting palliative stage with arterial shunt has also been recognized as a risk factor for LV dysfunction(9).

Over decades, the surgical approach has changed from the two-stage repair using right ventriculotomy and TAP to a transatrial-transpulmonary technique as a primary intention(54).

## **2.3 MODIFIED HISTORY AND FOLLOW-UP**

### **2.3.1 EARLY AND LATE MORTALITY**

There has been a drastic change in the operative mortality of Fallot surgery. Early mortality rates were as high as 14% in the early days of surgery. More recent studies have revealed a postoperative mortality of only 0% to 2%, and during the past 15 to 20 years the operative mortality rate has often been reported as close to zero (43, 55-58).

Late survival of repaired TOF patients up to 20 postoperative years has been reported to be 80% to 86% after surgery performed in the earlier surgical era (1958-1989) (43, 55, 56). According to a late hazard model, approximately 90% of patients with TOF corrected in the late 1980s and early 1990s are likely to survive into the fifth decade of life (45). Table 3 summarizes the results of 8 studies that have reported early and late survival of TOF patients.

**Table 3.**                    *Mortality in TOF patients according to the literature*

Study	Hickey et al.	Raissadat et al.	Eriksen et al.	Raissadat et al.	Eriksen et al.	Kirsch et al.	Cuyppers et al.	Cobanoglu et al.	Murphy et al.	Bacha et al.
<b>Number of patients</b>	1181	1081	349	226	218	277	136	63	57	57
<b>Operative years</b>	1960-1998	1953-2009	1990-2011	2000-2009	1971-1989	1995-2009	1968-1980	1981-1995	1955-1960	1972-1977
<b>Early survival (30 days after repair)</b>	90 %	94 %	98 %	99 %	92 %	100 %	84 %	94 %	na	86 %
<b>Late survival of early survivors</b>										
10 years	95 %	96 %	-	-	-	100 %	98 %	-	-	100 %
15 years	-	-	96 %	-	89 %	-	-	95 %	-	100 %
20 years	92 %	91 %	-	-	-	-	96 %	-	-	100 %
30 years	90 %	82 %	-	-	-	-	92 %	-	90-93%	98 %
40 years	87 %	75 %	-	-	-	-	86 %	-	-	-
50 years	-	59 %	-	-	-	-	-	-	-	-

### **2.3.2 CAUSES BEHIND LATE MORBIDITY AND MORTALITY**

Although the outcome of these patients has improved dramatically over the last decades, the long-term prognosis is still compromised by important chronic sequelae such as RV scarring, dysfunction, dilation, and arrhythmias, leading to higher morbidity and mortality than in their peers (59, 60). Surgical repair of RVOT obstruction often results in PR causing chronic volume loading and eventually RV dilatation and deterioration of function(61-65).

#### **2.3.2.1 Pulmonary valve regurgitation**

In the long term, these patients may demonstrate progressive PR with RV dilation and dysfunction, which are known to be important determinants of adverse late outcomes (63, 65-67). In a study by Shimazaki et al., isolated pulmonary incompetence had a negative correlation with symptom-free survival. This patient cohort was remarkable in that almost no complications were reported for the first 30 years of life but after that rapidly progressing RV failure, sudden death, and exercise intolerance were observed(68). Impaired exercise tolerance, ventricular arrhythmia, and sudden death have all been reported as secondary complications of PR (62, 69, 70).

#### **2.3.2.2 Biventricular dysfunction**

Although the RV has been the focus, the biventricular function and LV have been under active examination in recent years and emerging awareness has raised their importance in late outcomes of TOF. LV dysfunction has been reported as late sequelae in 20% of TOF patients. On the other hand, patients with normal RV ejection fraction (EF) were more likely to have normal LV function(71). Therefore, a strong correlation between RV and LV EFs has been documented in patients with repaired TOF(72).

Late deterioration of RV and LV function has been an increasing concern during the current millennium(71, 73). A report by Cuypers stated an impairment of systolic RV function in 75% and systolic LV function in 50% of the patients with a median follow-up time of 36 years after repair(74). This concomitant dysfunction of the left heart appears to increase heart failure and mortality in these patients (63, 71, 72, 75). The reasons behind LV dysfunction in TOF patients have been under active examination. In one study, LV dysfunction was shown to be affected by preoperative hypoxaemia when hypoxaemia was evaluated by six parameters: preoperative systemic oxygen saturation, pre-operative haematocrit, LV/RV pressure ratios, hypercyanotic spells, one-stage or two-stage repair, and age at correction(76). Impaired ventricular-ventricular interaction is another possible contributor to LV dysfunction. In a study of Weyman et al., dilated RV was shown to cause displacement of interventricular septum and to change the shape of the septum and LV(77). Another study demonstrated altered LV rotation in

relation to RV volume load, suggesting the presence of ventricular-ventricular interactions(78). Tretter et al. divided these interactions into three categories: (i) mechanical coupling, which included shared aggregated cardiomyocytes, shared interventricular septum, shared pericardial space, and serial circuits; (ii) electromechanical coupling; and (iii) neurohormonal coupling by myocardial fibrogenesis. Similar mechanisms have been described by several other authors (79, 80).

In the postoperative phase of repaired TOF, chronic pulmonary regurgitation causes profuse diastolic filling of the RV with dilation (81, 82). Accordingly, as many as 20% of late survivors of TOF develop a concurrent LV dysfunction, thus making this an important factor in the patient's late outcome (71). PVR has been reported to improve LV EF(82).

### **2.3.2.3 Rhythm disturbances and sudden death**

Adult patients with TOF have a relatively high risk of tachyarrhythmias and prevalence increases with age, especially with atrial fibrillation and ventricular tachycardia(62, 83). In a study of Khairy et al., TOF patients with an average postoperative follow-up time of 32 years had a prevalence of sustained tachyarrhythmia of 29.9%. Ventricular tachyarrhythmia (mostly ventricular tachycardia) was present in 14.6% and atrial fibrillation in 7.4% of these patients. In particular, the prevalence of these two disturbances increased with age and markedly after 45 years. The authors reported that these arrhythmias were associated with LV rather than RV function and especially with LV diastolic dysfunction(84). A remarkably lower arrhythmia prevalence of 10% was reported in a Japanese multi-institutional study(85).

TOF patients have a 0.15% to 0.2% risk of SCD(9, 86). Therefore, antiarrhythmic interventions are often needed(87). In a cohort of 408 patients, freedom from arrhythmia intervention was 78.6% at 32 years after repair; implanted cardioverter-defibrillators were used in 10.4% and pacemaker in 7.9% of these patients(84). Indications for ICD were syncope, prolonged QRS, previous ventricular tachycardia, and severe systolic dysfunction of RV or LV. In a study of Bokma et al., PVR did not reduce the rate of SCD after a 5.3 years of follow-up(88)

An overview of late complications with prevalence and annual risks is presented in table 4.

**Table 4.** Late complications of TOF (modified from Baumgartner et al. ((9))

<b>1. Pulmonary regurgitation</b>	<ul style="list-style-type: none"> <li>• almost always develops, especially after TAP repair</li> <li>• well tolerated for years</li> <li>• when severe and chronic, leads to RV dilation and dysfunction sometimes augmented by pulmonary artery stenoses</li> </ul>
<b>2. Residual RVOTO</b>	<ul style="list-style-type: none"> <li>• prevalence of ~40%</li> <li>• can occur at infundibulum, valvar level, at pulmonary trunk, distally (even in distal parts of the pulmonary branch arteries)</li> </ul>
<b>3. Residual VSD</b>	<ul style="list-style-type: none"> <li>• prevalence of ~10%</li> <li>• due to rupture or failure of VSD closure, LV volume overload possible</li> </ul>
<b>4. Aortic root dilation with aortic regurgitation</b>	<ul style="list-style-type: none"> <li>• often progressive, prevalence of ~15%</li> </ul>
<b>5. LV dysfunction</b>	<ul style="list-style-type: none"> <li>• prevalence of ~20-50%</li> <li>• multiple causes, for example intraoperative hypoxemia, impaired ventricular-ventricular interaction and aortic regurgitation</li> <li>• long-lasting palliative stage with arterial shunt increases risk</li> </ul>
<b>6. Ventricular tachycardias</b>	<ul style="list-style-type: none"> <li>• annual risk of 0.2%</li> <li>• relates to haemodynamic problems</li> <li>• risk increases as follow-up time gets longer</li> </ul>
<b>7. Sudden cardiac death</b>	<ul style="list-style-type: none"> <li>• annual risk of 0.15%</li> <li>• caused mostly by ventricular tachycardias or ventricular fibrillation</li> <li>• causes approximately one third of all TOF late deaths.</li> </ul>

### 2.3.3 POST-OPERATIVE FOLLOW-UP AND IMAGING

According to the European Society of Cardiology, all post-operative TOF patients should have a regular cardiological follow-up at a specialized clinic. This visit is recommended to be annual but can also be less frequent with patients at the milder end of the spectrum with stable haemodynamic condition. The evaluation should always look for the late complications presented in Table 4. Echocardiography should be performed at every visit and patients should be referred to CMR on a regular basis (9).

### **2.3.3.1 Imaging modalities tetralogy of Fallot**

An optimal imaging modality for late follow-up of TOF would allow a thorough assessment of all its morphological and functional abnormalities. With an ideal tool, RV volume and pressure overload, valve regurgitations or stenosis, and RV and LV dysfunction could be adequately measured. Possible myocardial scarring, RV lesions, fibrosis, and associated anomalies (such as aortic root dilation) should also be assessed. Such a modality should be cost efficient, easily available, and should not expose to ionizing radiation(89).

No single imaging modality fulfils these criteria and therefore at least four different tools are used for the late follow-up of TOF patients: (i) echocardiography, (ii) CMR, (iii) cardiac catheterization, and (iv) cardiovascular computed tomography.

### **2.3.3.2 Echocardiography**

Transthoracic echocardiography (TTE) is the first-line imaging examination in TOF both pre- and postoperatively. TTE is safe, causes no ionizing radiation, is easy to reproduce, and clinicians have a good level of expertise using it. RV and LV size and function, valvular stenosis, and regurgitation can be assessed by TTE. TTE yields haemodynamic estimates of RV and pulmonary pressure(89, 90). Advanced techniques, such as velocity vector imaging and speckle tracking imaging, enable early assessment of myocardial deformation and global and regional RV function. However, the use of these methods lack standardization for diagnostics (91).

### **2.3.3.3 Cardiac magnetic resonance**

Although pre-operative evaluation by echocardiography before the initial surgery is usually sufficient to demonstrate the surgical conditions, during the last two decades CMR has become the gold standard of postoperative imaging assessment of TOF patients(92). CMR allows reliable quantitative assessment of both RV and LV volumes, mass, and function(93-95). It also offers a possibility to study the pulmonary arterial branches and atrial function and volume. CMR is not dependent on ideal position of the heart in the thoracic cavity. As opposed to ultrasound, CMR also gives a full view to the right ventricular outflow tract. The volumetric assessment is performed manually and endocardial contours are drawn from both end systole and end diastole. EF is calculated from these measurements. Pulmonary and aortic regurgitation can be studied by using velocity mapping. PR can also be assessed by subtracting LV stroke volume and possible aortic regurgitation volume from RV stroke volume. CMR also allows precise evaluations of the aortic root and aortic insufficiency and permits quantifications of the distribution of flow to the left and right pulmonary artery.



#### **2.3.3.4 CMR Feature Tracking**

Strain and strain rate are techniques used in ultrasound and CMR and provide an on-site means to assess myocardial wall motion. Longitudinal strain measures the longitudinal shortening of the myocardium in the base-apex direction (negative value), circumferential strain measures the fibres shortening at transverse plane (negative value), and radial strain is used to describe myocardial motion towards the centre of the ventricular cavity (positive value). Strain rate is the rate of shortening of the length (1/s) and can be either systolic or diastolic (96, 97).

By using ultrasound-based myocardial deformation imaging, LV early diastolic radial and circumferential strain rates (81) and LV systolic measures have been shown to be affected by RV dilation and pulmonary regurgitation despite preserved LVEF (98, 99). However, diastolic strain parameters have been difficult to assess using CMR tagging due to dephasing of magnetization. The non-rigid elastic registration-based FT used in this work has been shown to be reproducible and not be influenced by the level of training (100). CMR-FT provides an accurate and rapid assessment of both atrial and ventricular strain. CMR-FT is much less time consuming, does not require additional imaging sequences, and has better temporal resolution (101) when compared with myocardial tagging.

#### **2.3.3.5 Late gadolinium enhancement**

Late gadolinium enhancement (LGE) is a diagnostic tool to detect scars and is based on the different distributions of gadolinium agent in different types of tissues. Contrast agent is distributed in the extracellular spaces but does not enter myocardial cells in physiological conditions. LGE occurs in pathological conditions either when the extracellular space of the tissue enlarges or the membranes of the myocardial cells are damaged, thus causing intracellular distribution of the gadolinium agent (102).

The LGE technique has been used to assess ischaemic and non-ischaemic heart disease and has promoted the understanding of LV dysfunction and the pathophysiology of these diseases (103-106). The histologic base of LGE CMR imaging has been previously validated in studies of hypertrophic cardiomyopathy and cardiac amyloidosis (107, 108). Adverse clinical markers, for example ventricular dysfunction and arrhythmias, have been shown to correlate with LGE in an adult population of TOF (109).

In clinical practice, LGE is assessed based on visual estimations and several grading protocols exist for diagnostics (109, 110). Some algorithms to assess LGE have also been developed and studied (111, 112).

## 2.4 RE-OPERATIONS AND INTERVENTIONS AFTER TOF REPAIR

### 2.4.1 PULMONARY VALVE REPLACEMENT

The post-operative phase of TOF patients is compromised by substantial morbidity. Due to pulmonary stenosis-relieving surgery, long-lasting PR leads to RV and LV dysfunction and often requires a re-operation to reconstruct the outflow tract of RV by replacing the pulmonary valve(62, 74, 113). The surgery is often performed by using valve homografts(93). PVR is known to reduce the size of the RV, stabilize QRS duration, and can reduce the risk of ventricular tachycardia(114, 115). LV function has also been reported to improve after PVR in paediatric and adolescent TOF patients(78, 82). Despite these results, the potential of RV to recover after PVR is possibly compromised in the adult population(116).

All patients who suffer right heart failure, have overt symptoms of exercise intolerance, or have symptomatic ventricular tachycardia should be candidates for surgery. In addition, there are many borderline patients who do not fulfil these criteria but would still benefit from the surgery(9).

Therrien et al. reported results from two series of PVR patients. In the first study, adult patients with a mean age of 34 years and grossly dilated RVs were shown to benefit from the operation at 2.4 years after the surgery. No significant PR was noted and the reported exercise capacity had improved. However, RV contractility and dimensions were not improved and tested exercise capacity was not improved(116). In another study with younger patients and lower degree of PR, both RVEDV and RVESV were decreased but RV EF remained unchanged at 21 months after PVR(116, 117). These authors suggested operative threshold values of RVEDV 170ml/m<sup>2</sup> and RVESV 85ml/m<sup>2</sup> for PVR. Essentially similar thresholds have been reported by other authors(118, 119). According to the European Society of Cardiology, PVR should be performed if the patient has symptoms and PR or stenosis is severe (systolic RV pressure >60 mmHg and tricuspid regurgitation (TR) velocity of >3.5 m/s). If the patient has no symptoms, PVR is indicated if the tested exercise capacity is impaired, RV dilation or dysfunction is progressive, tricuspid valve regurgitation is at least moderate, or RVOTO is present with RV systolic pressure of >80 mmHg. Other indications are sustained atrial or ventricular tachycardia(9). The American Heart Association states that PVR should be considered if two of the following criteria are met: (i) RV end diastolic volume (RVEDV)  $\geq 160\text{ml/m}^2$  + RV end systolic volume (RVESV)  $\geq 80\text{ml/m}^2$ , (ii) mild or poor RV or LV dysfunction, (iii) RVEDV more than twice the LV end diastolic volume (LVEDV), (iv) RV systolic pressure 2/3 or greater than the systemic pressure, or (v) progressively impaired tested exercise capacity(120).

Despite these thresholds, several questions related to the timing of PVR remain unanswered. For example, it is unclear how to treat an asymptomatic

patient with a threshold-size RV(121). Surgery itself is of low risk but potential complications still exist and the implanted valve may need a new replacement later in life (8, 122). In addition, subjective symptoms and exercise capacity are not shown to correlate, which makes decision-making even more difficult(8). There is no sufficient data about the functional benefits of surgery. Exercise performance is shown to improve after PVR but does not seem to correlate with ventricular remodelling in children and adults (123-125). Therefore, definitive data and guidelines for the timing of PVR are still absent. For some patients, PVR might never be necessary. Frigiola et al. suggested that patients surviving to 35 years of age with a normal exercise capacity could have had a definitive primary repair(126).

Aortic valve replacement is to be considered with severe aortic regurgitation when symptoms or LV dysfunction are present. If residual VSD is diagnosed, the closure is indicated if patient shows LV volume overload or patient is undergoing PVR(9).

#### **2.4.2 CATHETER-BASED THERAPY**

Transcatheter interventions are an important treatment option for postoperative TOF patients with RVOTO dysfunction. Transcatheter PVR (TPVR) is commonly done years after re-construction of RVOTO and is done with an adequate-sized homograft. This has been reported to be a feasible and beneficial technique especially when the patient has obstructive or mixed type of disease rather than severe RV dilation with abundant PR(127). The Melody valve (Medtronic, Inc., USA) is the only transcatheter pulmonary valve (TPV) approved for this indication by the FDA and in EU. Trials on other valves are in progress and only available in these settings(120). No criteria for RV size or function are established for TPVR and surgical PVR criteria are often used for guidance when assessing these patients. A lower risk of complications and faster postoperative recovery have often resulted in lower thresholds for this procedure. The American Heart Association recommends considering TPVR when at least moderate PR of RVOT conduit is present(128). In addition, recent reports support a more active approach to both PR and PS with lower than previous thresholds for intervention(51, 93, 127).

### **2.5 GENETICS, PREGNANCY AND SOCIAL OUTCOME**

#### **2.5.1 GENETICS**

The aetiology of TOF is multifactorial(16). It is most often considered to be sporadic even though the siblings of a TOF patient have an approximate 3% of recurrence risk if no other first-degree relatives with congenital heart defects exist(8). Knowledge about genetic abnormalities has increased vastly during the last two decades. Up to 25% of the TOF patients have been shown to have

chromosomal abnormalities, with trisomy 21 and microdeletion of the q11 region of chromosome 22 (22q11 microdeletion) being the most common (16). In general, the prevalence of this disorder is 0.025%(129). Some authors suggest that the 22q11 microdeletion alone is present in up to 25% of TOF patients(17). The presence of genetic abnormalities has been shown to affect the outcome of TOF after surgical repair (130) and therefore it has been suggested that after primary diagnosis of TOF all patients should undertake an investigation with fluorescence in-situ hybridization to exclude 22q11 microdeletion(17). This microdeletion is commonly diagnosed with a syndrome. The most severe type is DiGeorge syndrome with associated palatal abnormalities, learning disabilities, immune deficiencies, dysmorphic facial features and hypocalcaemia. A less severe 22q11 microdeletion-associated syndrome is velocardiofacial syndrome, where no immune deficiencies or hypocalcaemia typical of DiGeorge syndrome exist(131). Therefore, only 6% of TOF patients have a 22q11 microdeletion without any associated anomaly or syndrome(132). CATCH-22 is associated with several neuropsychiatric disturbances, such as attention deficit/hyperactivity disorder, anxiety, autism, depression, and bipolar disorder and psychotic disorders(129).

### **2.5.2 PREGNANCY OF THE POST-OPERATIVE PATIENTS**

Pregnancy is mostly well tolerated among women with TOF (133, 134). The risk of foetal loss and an increased proportion of congenital anomalies in the offspring are reported adverse foetal outcomes(135). Women with good haemodynamics, no symptoms, and only mildly dilated RV can expect a pregnancy outcome comparable to their healthy peers(133). Patients with RVOT obstruction, severe PR, and RV dysfunction can suffer from right heart failure and arrhythmias due to increased volume load during pregnancy (13, 135). Therefore, when these patients are consulted before pregnancy, several authors suggest considering PVR before pregnancy(135, 136). Vaginal delivery is the recommended mode of delivery, cardiac function should be carefully monitored by a specialist, and labour should happen in a tertiary unit for high-risk mothers(8, 136-138). According to the modified WHO classification of maternal cardiovascular risk, TOF is in class two with a small increase in maternal mortality and moderate increase in morbidity risk(139). The European Society of Cardiology recommends cardiological follow-up for these patients once every trimester(136).

### **2.5.3 EDUCATION AND QUALITY OF LIFE**

It has been reported that patients with cyanotic defects (study population of 68% TOF, 24% TGA, 8% UVH) have a lower rate of university level of education when compared to the general population (3% vs. 7%). No statistical differences were found in rates of compulsory or vocational education rates

between this study population and healthy controls. When patients with significant mental retardation were excluded, no difference was found in occupational status of these patients(140). When personal health assessment was studied in adult population after TOF repair, excellent or good status was reported in 82% vs. 90% when compared to the normal population(141). The number of patients having offspring was slightly lower than expected (32% vs. 39%,  $p < 0.05$ ). Marital status was similar to the general population(140).

### 3 OBJECTIVES

1. To establish population-based evaluation of the long-term results after TOF surgery in Finland starting from the first repair in 1962.
2. To evaluate if LGE, suggestive of fibrosis, is present in paediatric TOF patients and if it relates to markers of adverse outcome.
3. To study the mechanisms of how chronic PR affects RV and LV haemodynamics and myocardial function.
4. To study whether myocardial function and ventricular haemodynamics differ after transannular patching in comparison to valve-sparing procedures.

## 4 METHODS

### 4.1 STUDY I: SURGERY OF TETRALOGY OF FALLOT IN FINLAND

#### 4.1.1 SURGICAL TECHNIQUES TO REPAIR TOF

During the first decade of Finnish TOF surgery (1962-1969), the average age at repair was  $9.4 \pm 3.0$  years. During later decades we observed a gradual shift of operative ages towards early childhood and in the current millennium (2000-2007) repair was performed at the age of seven months. Today, it is widely accepted that the long-lasting palliative stage is detrimental to the heart and causes RV dilation and biventricular dysfunction. Accordingly, most centres prefer to repair TOF at approximately 6 months of age. In our institution, the surgery of the first decades was performed via ventriculotomy as the transatrial approach was introduced only in the 1980s and became a primary method of choice in the 1990s. Perioperative care and intensive care of TOF patients have also taken large leaps since the first days of surgery and partly explain the improved early and late outcome of these patients.

#### 4.1.2 PATIENT DATA

Patient data for the analysis was collected from the research database of paediatric cardiac surgery and additionally from hospital surgical logs, diagnosis cards, and computer files. The Research Registry of Paediatric Cardiac Surgery (Melba Group Helsinki) is a specially designed Filemaker-based database (Filemaker Pro version 11.0 v1, Filemaker Inc., CA, USA). Although paediatric cardiac surgery was centralized to Helsinki University Hospital in 1997, the registry contains all data of surgically operated paediatric cardiac patients in Finland and contains surgical data from the year 1953 to now.

The study was closed on 24 of October 2012. To determine current patient status and dates of death and emigration, data were obtained from the Finnish Population Register Centre. For the study, all patients with a primary diagnosis of either TOF or DORV of TOF type found from the Research Registry of Paediatric Cardiac Surgery were included. Pulmonary atresia patients were excluded. This data query identified 705 patients who had undergone surgery for TOF between 1962 and 2007. The patients remaining in palliative stage ( $n = 75$ ) and patients whose surgical operation took place after 15 years of age ( $n = 30$ ) were excluded from the study, leaving 600 patients for the final data analysis. The Finnish Population Register Centre registers all citizens with an unique social security number, which provided a

reliable method to identify and gather outcome data of our study population. Complete follow-up data were available for 595 patients (99%). Only 2 patients were lost to the follow-up and the follow-up ended prematurely in 3 patients due to emigration. In the survival analysis, the emigration day was considered as the last day of the follow-up for these patients. The characteristics of the study population is presented in Table 5.

**Table 5.** *Characteristics of study population*

<b>Total number of TOF surgical patients (n)</b>	705
<b>Patients remaining in palliative stage (n)</b>	75
<b>Patients operated after 15 years of age (n)</b>	30
<b>Total number of enrolled patients (n)</b>	600
<b>Operated between (years)</b>	1960-2012
<b>Alive at closing day (n)</b>	514
<b>Dead by closing day (n)</b>	82
<b>Lost to follow-up (n)</b>	4
<b>Age at correction</b>	
Primary intention (mean age; years)	3.4 ± 3.7
Previously palliated (mean age; years)	5.7 ± 4.7
<b>Transannular patch used (n)</b>	191

#### **4.1.3 MORTALITY**

Deaths within 30 days of surgery were considered early. The causes of late death were sought from death certificates obtained from Statistics Finland. For data analysis, deaths were divided by their main cause into congenital heart defect (CHD)-related and non-CHD-related deaths. Therefore, all patients with diseases with ICD-10 (International Classification of Diseases-



10) diagnosis numbers Q20 to Q28 (in old cases ICD-9 numbers 745–747) were included in the CHD-related group. Patients with any other causes of death were classified as non-CHD related. We used a previously established classification of the cardiac causes of death to divide the CHD-related deaths into four categories: heart failure, sudden death, perioperative, and other cardiovascular death (142). SCD was defined as death (or irreversible deterioration before death) due to cardiovascular causes within 1 h of onset of symptoms or unwitnessed death during sleep(143). For perioperative deaths, all early (within 30 days) deaths due to patient's first, second, or third re-operation were included. The other cardiovascular death was a group that included all CHD-related deaths that could not be classified into the three groups mentioned above.

#### **4.1.4 RELIEF OF RVOT OBSTRUCTION**

From our research database of paediatric cardiac surgery, we were able to extract surgical data and to define the method of RVOT reconstruction in 551 patients (92%) (Table 8). Despite the common congenital anomaly, the technique was always tailored for the specific patient according to the morphology observed on-site. The use of TAP is an effective method to relieve pulmonary stenosis but always results in permanent PR. The use of TAP was always an intraoperative decision. The pressure ratio between RV and LV was determined during the procedure. If the ratio was  $>0.7$  and if the surgeon observed the residual stenosis at the annular level, the annulus could not be preserved and a TAP was inserted.

## **4.2 STUDIES II-IV: THE HEARTS OF PAEDIATRIC AND ADOLESCENT TOF PATIENTS**

### **4.2.1 PATIENT COHORT**

#### **4.2.1.1 Recruitment**

Altogether 48 patients with TOF were included. The patients were referred to the study by a paediatric cardiologist due to echocardiographic findings suggesting significant PR and increased RV size. A total of 42 patients arrived from the Helsinki University Hospital district, serving a population base of 1.7 million. Paediatric cardiologists from other hospitals referred 6 patients to the study according to the same criteria. For full benefit to the patients, their less comprehensive annual ambulatory visit was replaced with the study protocol and no additional visits were needed.

#### **4.2.1.2 Surgical data**

Patients were operated between 1990 to 2003. During the surgery, cardiopulmonary bypass with aortic crossclamp was used. Cold blood cardioplegia was used for myocardial protection. During the first 7 years, 20 patients were repaired and 7 (35%) received TAP. During the last 7 years, 28 of patients were repaired and 20 (71%) received TAP. Initially, palliation was performed altogether on 8 patients over both 7-year surgery periods.

#### **4.2.2 HEALTHY CONTROLS**

Healthy volunteers were recruited from local schools, girl guides, boy scouts, and family members of the healthcare staff. Forty-four healthy age- and gender-matched paediatric and adolescent volunteers were recruited for the study. The following admission criteria were used: (i) no medical history of any cardiovascular disease and (ii) no other pre-existing condition that would affect the cardiovascular system.

#### **4.2.3 STUDY PROTOCOL**

A paediatric cardiologist performed a morphologic ultrasound, clinical examination, and ECG to exclude possible latent cardiac problems. CMR imaging was performed on all patients and healthy controls. Blood samples from a peripheral vein were drawn from all subjects.

**Table 6.** *Magnetic resonance imaging protocols in the study. \*LGE grading was performed according to our newly developed grading method (144).*

	Vendor	Method	Technical description
<b>MRI engine</b>	1.5T Achieva system (Philips Healthcare, The Netherlands)		5-channel cardiac coil.
<b>Ventricular volume analysis</b>	Philips ViewForum workstation (Philips Healthcare, The Netherlands)	Transaxial and left ventricle short axis cine imaging, manual planimetry	Balanced turbo field echo breath-hold. Slice thickness 5-8 mm, gap 20%, temporal resolution 26-43 ms. 30 temporal phases in short-axis, 25 temporal phases in long-axis direction
<b>Pulmonary flow and aortic regurgitation</b>	Philips ViewForum workstation (Philips Healthcare, The Netherlands).	Through plane phase contrast measurement.	A retrospectively gated free breathing acquisition, temporal resolution of 24 ms and VENC 200, slice thickness was 10 mm, TR 4.019, TE 2.427, ET 4
<b>Pulmonary regurgitation</b>	Philips ViewForum workstation (Philips Healthcare, The Netherlands).	Calculation from volumetric measurements of both ventricles	PR = RV stroke volume - LV stroke volume - Aortic regurgitation
<b>Lata gadolinium enhancement</b>	1.5T Achieva system (Philips Healthcare, The Netherlands), Dotarem*.	Transaxial and sagittal late enhancement images from both ventricles, visual assessment and grading of each segment according to the linear extent of enhanced myocardium*	Gd-DOTA, Gadoterate meglumine 279.3 mg/ml (Dotarem*) 0.2 ml/kg injection 10 min prior to imaging
<b>Atrial measurements</b>	Philips ViewForum workstation (Philips Healthcare, The Netherlands).	Transaxial and left ventricle short axis cine imaging, manual planimetry	Manual tracing of end diastolic and end systolic endocardial contours
<b>Strain analysis</b>	Segment software v.2.0 R5585 ( <a href="http://segment.heiberg.se">http://segment.heiberg.se</a> )	Feature tracking, performed retrospectively on short-axis and long-axis cine images	Manual drawing of the wall contours in the first cine image the end of diastole. Rest of the image sequence segmented automatically by the software, corrected manually if needed

#### 4.2.4 CMR IMAGING TECHNIQUES

The CMR study was performed using a 1.5T Philips Achieva System engine. Volumetric analysis was based on manual planimetry. When using CMR to study PR, it is possible to use either the difference of the ventricular stroke volumes (ml/m<sup>2</sup>) or mapping of phase-contrast of the main pulmonary artery flow (%). The use of stroke volume difference has been reported to better correlate with ventricular volumes(145, 146) and was preferred in our studies.

LGE grading was performed by visually assessing the images and a previously published RV LGE grading protocol that had seven RV segments, including the target locations of surgical repair, which served as a basis for our grading method (109).

For the atrial volume measurements, transaxial cine images were manually planimetryed according to a previously described method(147). The cyclic volume change was calculated by using atrial volumetric measurements by subtracting minimal atrial volume from maximum. Conduit volume refers to diastolic blood flow to the chambers while the atrial pump remains passive. This was assessed by subtracting the cyclic volume change from the LV stroke

volume. The combined preload volumes from the atria for each ventricle were calculated by adding the cyclic volume change to conduit volume.

CMR strain analysis was performed using Segment software® and FT was performed retrospectively by manually drawing the first cine image and the other sequences automatically by software.

We measured time-strain curves covering the entire cine image sequences. Peak systolic strain (%), peak systolic strain rate (%/s), and peak diastolic strain rate (%/s) were calculated from the curves. TOF patients have ventricular dyssynchrony and delayed RV contraction when compared with healthy controls(148, 149). Therefore it is difficult to compare the strain curve of a TOF patient and a healthy controls. To allow visual comparison of the strain curves we used heart rate correction for the RR-interval. We linearly corrected the RR-interval of the strain curves to match a heart rate of 68 (mean of the healthy controls). The correction is similar to Bazett's formula for heart rate corrected QT interval. Heart rate determines the duration of the RR-interval, and with no correction no temporal comparison between the strain curves would have been possible. CMR imaging methods, techniques, and protocols are summarized in Table 6.

#### **4.2.5 CHARACTERISTICS OF THE STUDY POPULATION (STUDIES II-IV)**

Our study patients were children and adolescents with a mean age of  $13.1 \pm 3.3$  years. Primary palliation prior to corrective surgery was performed on 16 (40%) patients. TAP was inserted in 24 (53%) patients. A re-operation after primary correction was needed for 6 patients (15%) during the follow-up time of the study (2007-2014).

The CMR was not comprehensive for all patients or controls because of insufficient image quality due to technical reasons or patient anxiety. Depending on the different CMR methods used in studies II to IV, some but different patients were rejected in each study because of poor image quality.

**Table 7.** *Characteristics of the study population (studies II-IV)*

	Patients	Controls	P
<b>n</b>	48	44	-
<b>Male gender, n (%)</b>	23 (61%)	27 (56%)	-
<b>Age (years)</b>	13.1 ± 3.2	13.8 ± 3.4	ns.
<b>Age at TOF repair (years)</b>	1.3 ± 1.1	-	-
<b>Follow-up time from TOF repair (years)</b>	11.9 ± 2.9	-	-
<b>Weight (kg)</b>	42.7 ± 14.7	50.5 ± 15.8	0.02
<b>Height (cm)</b>	152.2 ± 15.4	159.4 ± 16.2	0.03
<b>Body surface area (m<sup>2</sup>)</b>	1.3 ± 0.3	1.5 ± 0.3	0.02

### 4.3 STATISTICAL ANALYSIS

Statistical analysis was performed using both IBM SPSS Statistics 19 and 24 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 5.0a (GraphPad Software, Inc. San Diego, California, USA). All results are reported as mean±SD. Comparisons of continuous data between the groups were performed using an unpaired t test. Correlations were calculated by using Pearson correlation coefficient. A two-tailed P-value of less than 0.05 was considered statistically significant. Inter-observer variability was tested by using Spearman's test and the Bland-Altman method. Intra-observer variability between strain measurements was evaluated by using intraclass correlation coefficient (ICC).

We assessed the time-related mortality with survival analysis and used the life-table method. For survival analysis, we calculated one overall survival for all patients. We performed a separated analysis for patients operated on during the last four eras (1970–1979, 1980–1989, 1990–1999, and 2000–2007). The survival rates between patients with and without primary palliation were compared and the survival of patients with and without TAP was analysed. To evaluate the effects of different surgical methods on the need for re-operation, the event-free survival of the patients was also studied. For this analysis, death and re-operation were considered as events. Survival analyses of the study are presented as Kaplan-Meier plots.

The Wilcoxon (Gehan) paired test was used to compare survival with different groups. For the analysis of the proportion of TAP operations or re-operations after palliation, the  $\chi^2$  test was used.

#### **4.4 ETHICAL APPROVAL AND CONSENTS**

The Ethics Committee of the Children's Hospital of the Helsinki University Central Hospital approved the study. Written informed consent was obtained from all the participants or their parents.

## 5 RESULTS

### 5.1 SURGERY OF TETRALOGY OF FALLOT IN FINLAND (STUDY I)

#### 5.1.1 EARLY AND LATE RESULTS AND CAUSES OF DEATH

##### 5.1.1.1 Patients

We studied a 45-year period of surgery closing at the end of 2007, which included the first repair of TOF in Finland in 1962. During that time, repair (or total correction) was performed in 600 patients who were younger than 15 years at the time of the surgery. The closing day of the follow-up was the end of 2012. The study consisted of 10 517 patient-years and the mean follow-up time was  $23 \pm 12.1$  years (range 0-49.9 years). There was a 60% male predominance in our study population. On the closing day of the study, the mean age of the patients was  $25 \pm 14.5$  years (range 0.23-61 years). The follow-up rate was as high as 99.1%.

##### 5.1.1.2 Early mortality

In our study population we observed an 85.5% survival rate where 514 patients were alive and lived in Finland. Eighty-two patients succumbed, making the overall mortality 13.7%. Of these 82 deaths, a total of 40 (6.7%) were early ( $\leq 30$  days after corrective surgery) and 42 (7.0%) were late ( $> 30$  days after corrective surgery). The early mortality of the last two decades was only 1.5% and we did not observe early deaths after the year 2000.

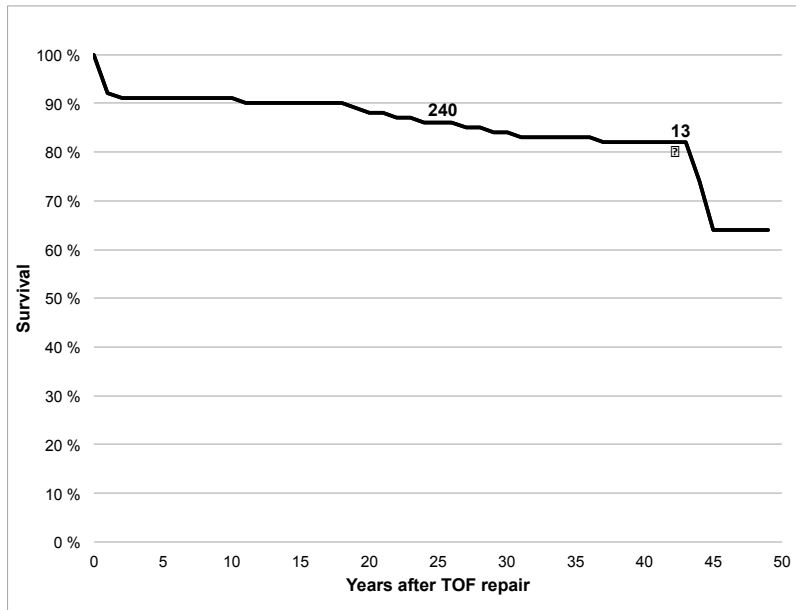
##### 5.1.1.3 Need for re-operation

According to our study, a total of 121 (20.1%) patients needed re-operation during the 23-year follow-up period. The most common intervention was PVR. There were 7 early deaths in this group, which in this study were reported as late deaths after total correction.

##### 5.1.1.4 Late survival

We observed a late survival rate of 86% in our study population. Survival of the first 5 years was 91%, 10 years 90%, 20 years 88%, and 40 years 83%. The late survival of our patients is presented in Figure 5.

**Figure 5** Overall survival of TOF patients (n=600). The numbers above the curves show the number of living patients 25 and 43 years after corrective operation. Early mortality is included. Modified from Ylitalo et al., Eur J Cardiothorac Surg 2015, with permission from Oxford University Press.



Excluding the first postoperative follow-up year after repair, our patients could expect an almost 100% survival rate during childhood as the first increment of mortality was seen in late adolescence. Thereafter, the attrition rate progressed initially slowly but escalated after 40 years of life (Figure 5).

#### **5.1.1.5 Causes of late mortality**

We identified the causes of death in all 82 patients. When examined in detail, we observed 66 deaths related to TOF and 11 deaths were unrelated to the heart. The exact causes of deaths are reported in Table 8.



**Table 8.** *Causes of death of the Finnish TOF population*

<b>Results</b>		<b>n</b>	<b>%</b>
<b>Alive</b>		<b>513</b>	<b>85.5</b>
<b>Death</b>		<b>82</b>	<b>13.7</b>
	Early mortality	40	
	Late mortality	42	
<b>Unknown</b>		<b>5</b>	<b>0.8</b>
	Emigrated	3	
	Lost to follow-up	2	
<b>Late mortality</b>			
	Early mortality in reoperations	<b>7</b>	<b>1.2</b>
	Late cardiac death	<b>19</b>	<b>3.2</b>
	Sudden death	13	
	Heart failure	5	
	Cardiovascular death	1	
	Late non-cardiac death	<b>11</b>	<b>1.8</b>
	Accident	2	
	Alcohol poisoning	2	
	Cancer	2	
	Suicide	2	
	Hydrocephalus	1	
	Epileptic attack	1	
	Pneumonia	1	
	Late death, unknown reason	<b>5</b>	<b>0.8</b>

In our present patient cohort, SCD had an incidence of 0.12% per patient-year and was the most common late cause of mortality related to cardiac reasons.

The two other late causes of cardiac deaths were heart failure and cardiovascular death, which included all CHD-related deaths that could not be classified into SCD or heart failure. We reported a 1.8% rate of mortality due to non-cardiac causes, including diverse reasons such as accidents, cancer, and suicide (Table 8).

## 5.1.2 THE METHOD OF RVOT RECONSTRUCTION

### 5.1.2.1 Transannular patch as a surgical technique

TAP was inserted in 191 (32%) of the repairs performed, pulmonary valve annulus was preserved in 60%, and the method could not be defined in 8% of the patients. Surgical data including the operative ages of different surgical eras are presented in Table 9.

**Table 9.** *Surgical data of study population*

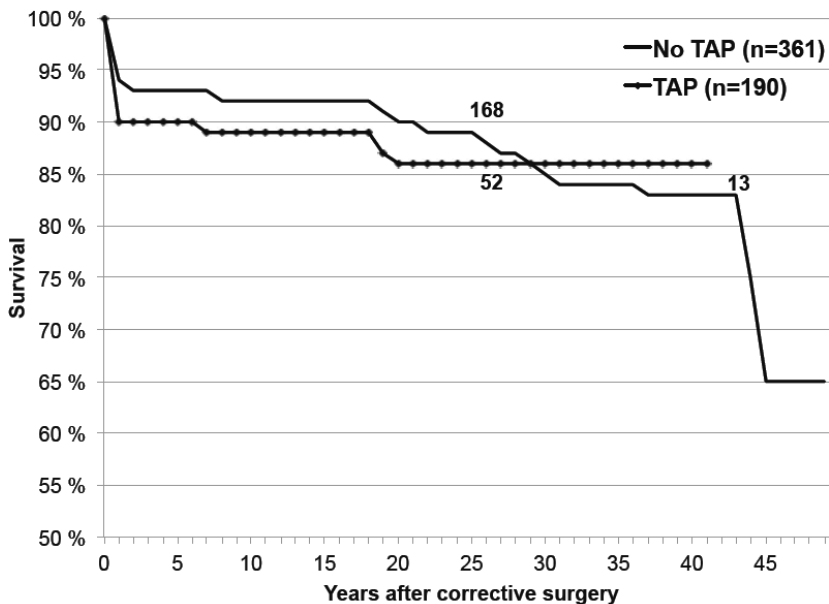
Primary procedures	n	%
Primary correction	451	75.2
Primary palliation	149	24.8
Transannular patch (TAP) used	190	31.7
TAP not used	361	60.2
Use of TAP unknown	49	8.2
Re-operations ( ≥1 )		
All patients	122	20.3
Patients primary corrected	67	14.9
Patients primary palliated	55	36.9
Patients with TAP	57	30.0
Patients with no TAP	58	16.1

Operative ages (years)	Mean	Median	Range
Age at correction	<b>3.9±4.1</b>	<b>2.0</b>	<b>0.02-15.0</b>
1962-1969	9.4±3.0	10.8	1.7-12.7
1970-1979	8.0±4.0	7.9	0.4-15.0
1980-1989	3.4±3.1	2.2	0.1-14.5
1990-1999	1.8±2.1	1.3	0.1-13.1
2000-2007	0.7±0.8	0.6	0.2-6.6
Age at correction (primary intention)	<b>3.4 ± 3.7</b>	<b>1.7</b>	<b>0.02-15.0</b>
Age at correction (previously palliated)	<b>5.7 ± 4.7</b>	<b>4.3</b>	<b>0.2-14.8</b>
Age at primary palliation	<b>1.4 ± 2.0</b>	<b>0.6</b>	<b>0.0-9.3</b>
Age at first re-operation	<b>14.1 ± 12.6</b>	<b>9.5</b>	<b>0.4-54.9</b>

### 5.1.2.2 Effects of TAP on early and late survival

We did not observe an increase in all-cause mortality in patients with TAP when compared to those whose pulmonary valve annulus was preserved (12.1% vs. 12.7%). The survival of TAP and non-TAP patients is presented in Figure 6.

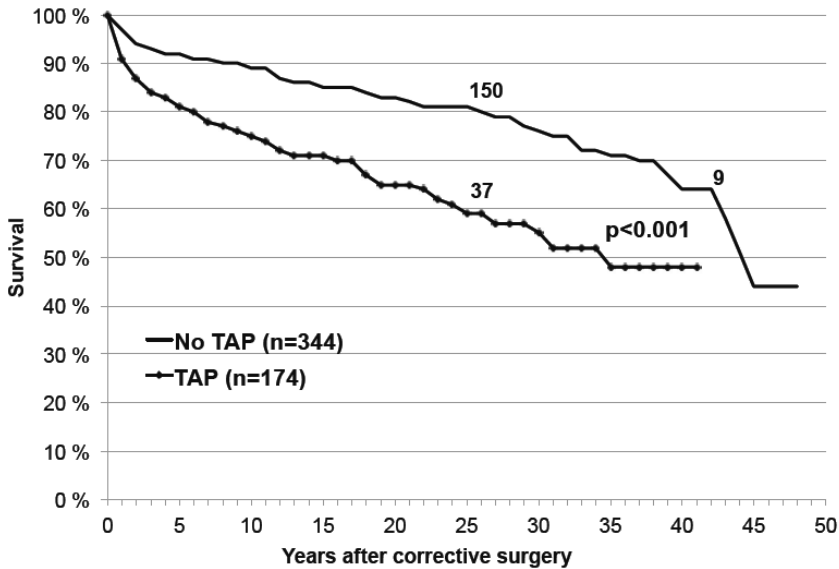
**Figure 6** Survival after TOF repair with or without transannular patch (=TAP or no TAP). Numbers above the curves show the number of living patients 25 and 43 years after corrective operation. Early mortality is included. Modified from Ylitalo et al., Eur J Cardiothorac Surg 2015, with permission from Oxford University Press.



### 5.1.2.3 TAP decreases event-free survival

We studied the significance of TAP on the time-related risk of re-operation after excluding early mortality. Both re-operation and death were considered as events in this analysis (Figure 7). We observed a significantly inferior event-free survival in patients if reconstruction of the RV outflow tract was performed by using TAP.

**Figure 7** Effect of TAP on event-free survival. Modified from Ylitalo et al., Eur J Cardiothorac Surg 2015, with permission from Oxford University Press.



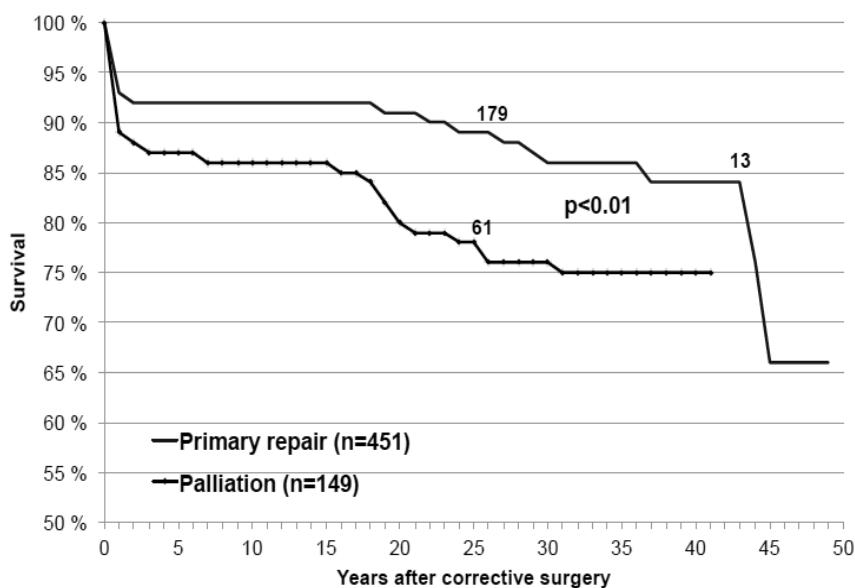
### 5.1.3 PRIMARY CORRECTION VS. PRIMARY PALLIATION

#### 5.1.3.1 Survival of primary palliated patients

In our study population, primary palliation was performed on 149 (25%) patients. The proportion of primary palliations over five consecutive decades was 71%, 21%, 15%, 25%, and 15%.

We observed a significantly inferior late survival of these patients when compared to those whose primary operation was repair (20.8% vs. 12.8%,  $P=0.007$ , respectively; Figure 8). The surgeon was less often able to preserve the pulmonary valve annulus during the correction if palliation had taken place previously (41% vs. 29%,  $P=0.001$ ). These patients more likely had a difficult original morphology or more severe pulmonary obstruction and thus needed an early palliation; therefore pulmonary valve preservation was not possible at repair.

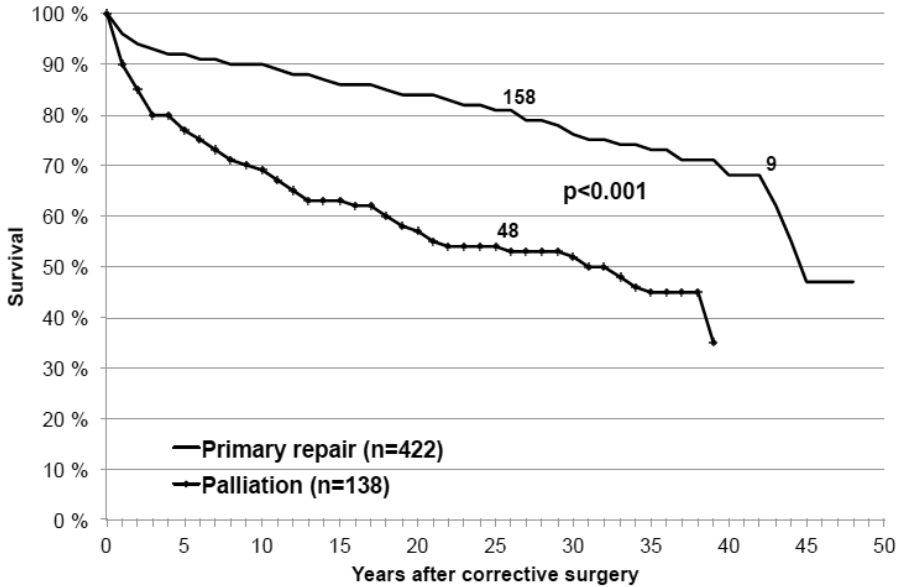
**Figure 8** Survival of patients with or without primary palliation. Numbers above the curves show the number of living patients 25 and 43 years after corrective operation. Early mortality is included. Modified from Ylitalo et al., Eur J Cardiothorac Surg 2015, with permission from Oxford University Press.



### 5.1.3.2 Primary palliation and re-operations

We also observed a higher rate of re-operations in this study group of patients with primary palliation (36.9% vs. 14.9%,  $P < 0.001$ ). The data on the freedom from re-operation or death after primary palliation and primary correction are shown in Figure 9.

**Figure 9** Event-free survival (event= re-operation or death) of TOF patients with or without primary palliation. Numbers above the curves show the number of living patients 25 and 43 years after corrective surgery. Early mortality is excluded. Modified from Ylitalo et al., Eur J Cardiothorac Surg 2015, with permission from Oxford University Press.



## 5.2 CARDIOVASCULAR MAGNETIC RESONANCE IMAGING OF TOF PATIENTS WITH PULMONARY REGURGITATION (STUDIES II-IV)

Patient history was assessed from patient charts and surgical logs. No time-related trends in perfusion times or aortic closure times were observed. All patients had right bundle branch block in their rest ECG recording.

### 5.2.1 GRADING OF PR AND FACTORS DETERMINING ITS DEGREE

PR was present in all study patients. The use of TAP had a clear effect on PR, as patients with TAP had mostly severe PR ( $>30\text{ml/m}^2$ ,  $n=11$ ) whereas patients with preserved pulmonary valve annulus had mostly non-severe PR ( $<30\text{ml/m}^2$ ,  $n=23$ , only 2 patients exceeding the limit). The mean PR of TAP patients was  $30.8\text{ ml/m}^2 \pm 10.2$  (range 16.7-59.4) and the mean PR for non-TAP

patients was  $9.8 \text{ ml/m}^2 \pm 10.3$  (range 0-31.8). We only observed negligible PR in control subjects.

### **5.2.1 RIGHT VENTRICULAR VOLUMES AND FUNCTION**

In study III we observed elevated RV volumes (both diastolic and systolic) when compared to control subjects ( $P < 0.0001$ ). PR also had an effect on RV stroke volume but had no effect on RVEF (table 10). Patients with PR  $< 30 \text{ ml/m}^2$  had comparable RV stroke volume as healthy subjects. RV sizes and functions are described in detail in Table 10.

**Table 10.** *Right ventricular volumes, function, and pulmonary regurgitation of patients with severe ( $>30\text{ml/m}^2$ ) and non-severe ( $\leq 30\text{ml/m}^2$ ) pulmonary regurgitation and healthy controls.*

Right ventricle	Patients with PR $>30\text{ml/m}^2$ , n = 13	Patients with PR $\leq 30\text{ml/m}^2$ , n=25	Controls n=48	p value PR $>30\text{ml/m}^2$ vs. PR $\leq 30\text{ml/m}^2$	p value PR $>30\text{ml/m}^2$ vs. controls	p value PR $\leq 30\text{ml/m}^2$ vs. controls
Ventricle preload from atria ( $\text{ml/m}^2$ )	44.9 $\pm$ 4.3	54.3 $\pm$ 8.0	58.9 $\pm$ 10.7	0.0004	<0.0001	ns
Ventricle preload from PR ( $\text{ml/m}^2$ )	37.0 $\pm$ 7.9	14.2 $\pm$ 10.6	1.2 $\pm$ 4.6	<0.0001	<0.0001	<0.0001
End diastolic volume ( $\text{ml/m}^2$ )	150.1 $\pm$ 22.0	126.3 $\pm$ 21.7	102.0 $\pm$ 17.1	<0.0001	<0.0001	0.0004
End systolic volume ( $\text{ml/m}^2$ )	85.5 $\pm$ 27.8	57.9 $\pm$ 15.9	43.1 $\pm$ 14.5	<0.0001	<0.0001	0.0001
Stroke volume ( $\text{ml/m}^2$ )	81.9 $\pm$ 10.8	68.4 $\pm$ 10.8	60.1 $\pm$ 10.8	0.0001	<0.0001	0.002
Ejection fraction (%)	55.4 $\pm$ 8.0	54.8 $\pm$ 5.5	59.2 $\pm$ 6.1	ns	ns	ns



### **5.2.2 LEFT VENTRICULAR PRELOADING, VOLUMES, AND FUNCTION**

In study III we observed smaller LV end diastolic and stroke volumes in rTOF resulting from abnormal LV filling. The left atrial maximum volume, cyclic volume change, and conduit volume were smaller when compared to healthy controls. When  $PR > 30 \text{ ml/m}^2$ , patients presented significantly diminished LV end diastolic volume, LV stroke volume, and LV EF when compared to the control subjects. Patients whose PR was  $< 30 \text{ ml/m}^2$  had LV volumes and EF similar to healthy subjects (Table 11).

**Table 11.** Left ventricular preloads, volumes, function, and pulmonary regurgitation of patients with severe ( $>30\text{ml/m}^2$ ) and non-severe ( $\leq 30\text{ml/m}^2$ ) pulmonary regurgitation and healthy controls.

Left ventricle	Patients with PR $>30\text{ml/m}^2$ , n = 13	Patients with PR $\leq 30\text{ml/m}^2$ , n=25	Controls n=48	p value PR $>30\text{ml/m}^2$ vs. PR $\leq 30\text{ml/m}^2$	p value PR $>30\text{ml/m}^2$ vs. controls	p value PR $\leq 30\text{ml/m}^2$ vs. controls
Ventricle preload from atria ( $\text{ml/m}^2$ )	44.1 $\pm$ 4.7	53.6 $\pm$ 8.8	58.9 $\pm$ 10.7	0.01	<0.0001	ns
Ventricle preload from AR ( $\text{ml/m}^2$ )	0.8 $\pm$ 1.3	0.7 $\pm$ 1.5	0	ns	ns	ns
End diastolic volume ( $\text{ml/m}^2$ )	80.8 $\pm$ 8.5	90.9 $\pm$ 18.9	94.6 $\pm$ 15.9	ns	0.008	ns
End systolic volume ( $\text{ml/m}^2$ )	35.9 $\pm$ 5.7	39.6 $\pm$ 9.6	35.7 $\pm$ 9.2	ns	ns	ns
Stroke volume ( $\text{ml/m}^2$ )	44.1 $\pm$ 4.7	53.6 $\pm$ 8.8	58.9 $\pm$ 10.7	0.0004	<0.0001	ns
Ejection fraction (%)	57.7 $\pm$ 5.8	59.3 $\pm$ 6.9	62.7 $\pm$ 6.9	ns	0.004	ns

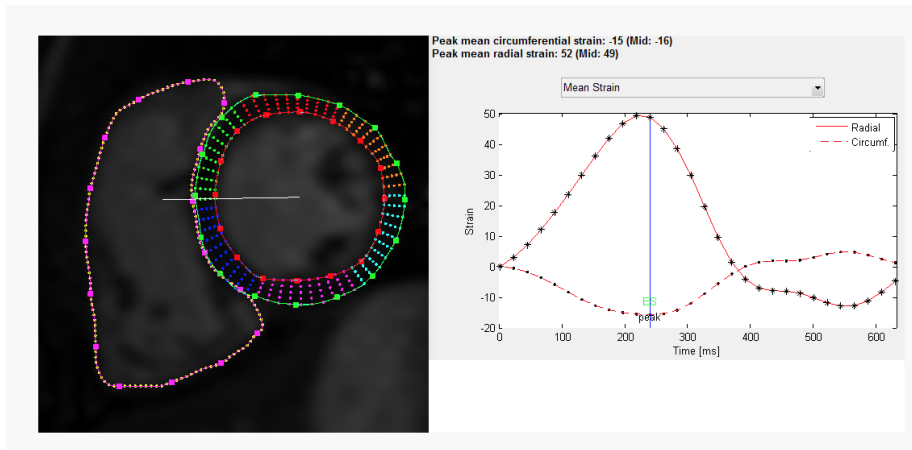
### 5.2.3 MYOCARDIAL CINETICS

#### 5.2.3.1 CMR Feature Tracking

CMR-FT is a novel method to assess wall motions and disturbances of both the RV and LV. In study IV, we chose to assess the myocardial function with CMR-FT, where the image quality is maintained throughout the cardiac cycle. Our intra-observer variability analysis agreed with this result. The analysis was performed by manually drawing the wall contours in the first cine image at the end of diastole (Figure 10).

**Figure 10** (i) Mid-ventricular short-axis view of the LV and RV in a patient with TOF at end diastole. LV epicardial and endocardial borders as well as RV endocardial borders have been manually drawn in the image.

(ii) The resulting strain curves for LV circumferential (dashed line) and radial strain (solid line). Different markers along the curves (· and \*) correspond to different time points in the cine image sequence (i.e., there are 30 temporal phases in the image sequence).



#### 5.2.3.2 Circumferential and longitudinal strains

When rTOF and controls were compared, we observed an increase in all RV circumferential measures (strain, systolic strain rate, and diastolic strain rate) of the patient group (Table 12).

RV peak longitudinal strain was significantly increased in rTOF patients with PR  $>30$  ml/m<sup>2</sup> when compared to those with PR  $<30$  ml/m<sup>2</sup> ( $-22.5\% \pm 2.7\%$  vs  $-19.7\% \pm 3.5\%$ ,  $P=0.018$ ) and controls ( $19.4 \pm 3.2\%$ ,  $P=0.007$ ).

No difference in RV peak longitudinal strain was present between rTOF patients with PR <30 ml/m<sup>2</sup> and controls. In rTOF patients, PR had a negative correlation with RV systolic longitudinal strain rate ( $R=-0.37$ ,  $P=0.030$ ) and a positive correlation with RV diastolic longitudinal strain rate ( $R=0.39$ ,  $P=0.021$ ). Thus, patients with florid PR had on average higher RV longitudinal peak strain in the rTOF population (Table 11). This was considered as a possible but appropriate compensation of the RV function.

**Table 12.** *RV circumferential and longitudinal strain data of TOF patients (TOF), healthy controls (Healthy), and TOF patients in two groups divided according to the severity of pulmonary regurgitation (TOF PR <30 ml/m<sup>2</sup> and TOF PR >30 ml/m<sup>2</sup>).*

Parameter	Healthy N=44	TOF N=40	P-value	TOF (PR < 30ml/m <sup>2</sup> ) N=29	TOF (PR > 30/m <sup>2</sup> ) N=11	P-value
<b>RV circumferential</b>						
Strain (%)	-11.5 ± 3.2	-16.6 ± 3.9	< 0.0001*	-16.7 ± 3.6	-17.0 ± 4.1	0.698
Systolic strain rate (%/s)	-59.9 ± 20.9	-79.8 ± 23.4	< 0.0001*	-77.9 ± 21.8	-84.8 ± 32.1	0.472
Diastolic strain rate (%/s)	60.8 ± 19.2	87.0 ± 33.0	< 0.0001*	84.4 ± 32.1	93.9 ± 35.7	0.447
<b>RV longitudinal</b>						
Strain (%)	-19.4 ± 3.2	-20.6 ± 3.5	0.147	-19.7 ± 3.5	-22.5 ± 2.9	0.018*
Systolic strain rate (%/s)	-83.5 ± 18.5	-99.3 ± 23.1	0.002*	-94.7 ± 20.2	-109.4 ± 26.6	0.122
Diastolic strain rate (%/s)	81.1 ± 26.9	106.7 ± 32.8	0.0001*	101.5 ± 27.1	124.4 ± 39.6	0.103

LV longitudinal diastolic strain rate was the only LV strain parameter to differ between rTOF patients and controls ( $65.9 \pm 19.1$  vs.  $81.9 \pm 31.1$ )

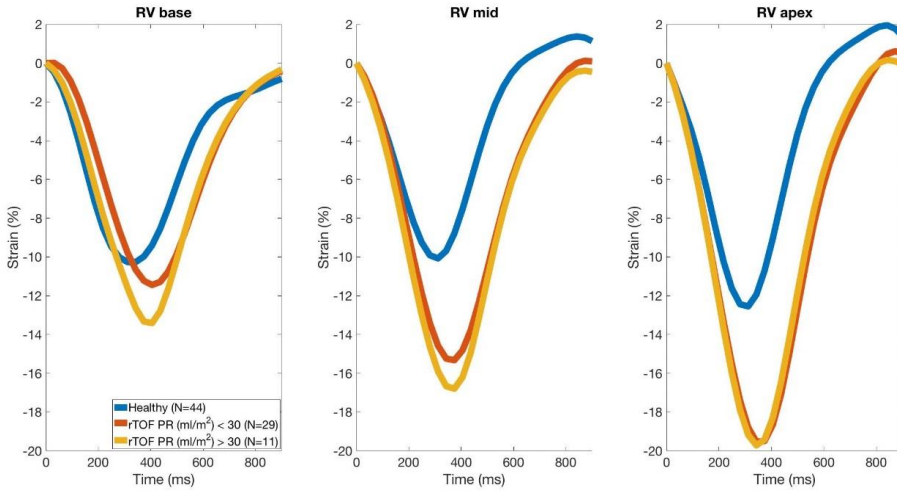
### 5.2.3.3 Segmental strain analysis

By grouping the circumferential strain measurements to apical, mid, and basal regions, we noticed that the peak strain values increased from base to apex in all study groups. Strain in our normal controls was similar at basal and mid-level and highest (on average 2.5% higher) in the apical plane as described previously (150). RV circumferential strain in different short-axis planes was measured and peak strain was significantly increased in all planes in the entire TOF population. The increase was highest at the mid-ventricular and apical levels ( $P < 0.0001$ ). There were no differences between the two TOF subgroups (Table 12 and Figure 11).

**Table 13.** *Segmental right ventricular circumferential strain of healthy controls, rTOF patients, and rTOF patients in two groups according to the severity of pulmonary regurgitation (TOF PR  $< 30$  ml/m<sup>2</sup> and TOF PR  $> 30$  ml/m<sup>2</sup>).*

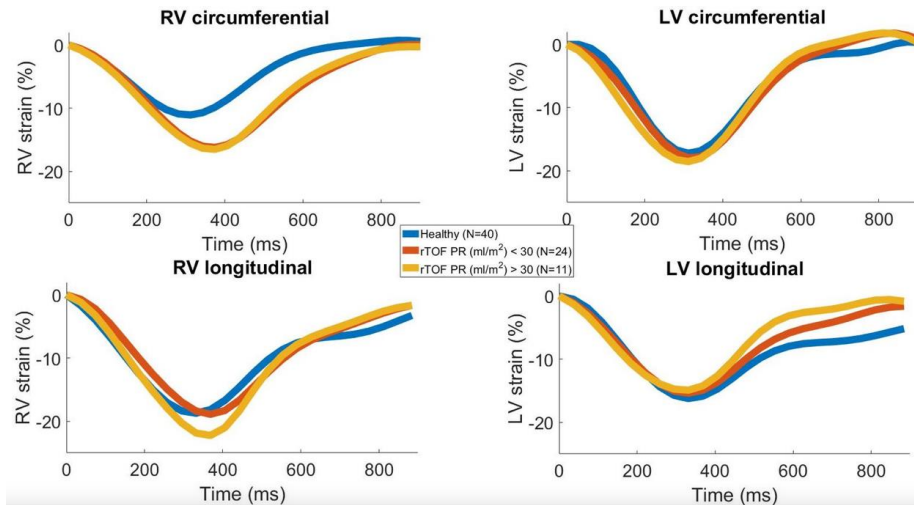
Right ventricle plane			
	Healthy (N=44)	TOF (N=40)	P-value
Base	$-11.2 \pm 2.9$	$-13.1 \pm 3.8$	0.01*
Mid	$-10.7 \pm 3.4$	$-16.8 \pm 4.2$	$< 0.0001^*$
Apex	$-13.5 \pm 4.2$	$-20.7 \pm 5.0$	$< 0.0001^*$
	TOF PR $< 30$ (N=29)	TOF PR $> 30$ (N=11)	P-value
Base	$-12.8 \pm 4.0$	$-13.9 \pm 3.1$	0.341
Mid	$-16.6 \pm 4.0$	$-17.3 \pm 5.0$	0.636
Apex	$-20.8 \pm 4.7$	$-20.4 \pm 6.0$	0.876

**Figure 11** Mean RV circumferential strain curves in basal, mid-ventricular, and apical planes with heart rate corrected to 68 (mean HR of healthy controls) in each group. LV=left ventricle, RV=right ventricle, PR=pulmonary regurgitation (ml/m<sup>2</sup>).



In comparison with healthy controls, the timing of both circumferential and longitudinal RV peak systolic strain was delayed. This was similar within the two patient groups. LV longitudinal strain in diastole returned to baseline faster in patients with TOF than in healthy subjects (Figure 12).

**Figure 12** Mean strain curves with heart rate corrected to 68 (mean HR of healthy controls) in each group. LV=left ventricle, RV=right ventricle, PR=pulmonary regurgitation



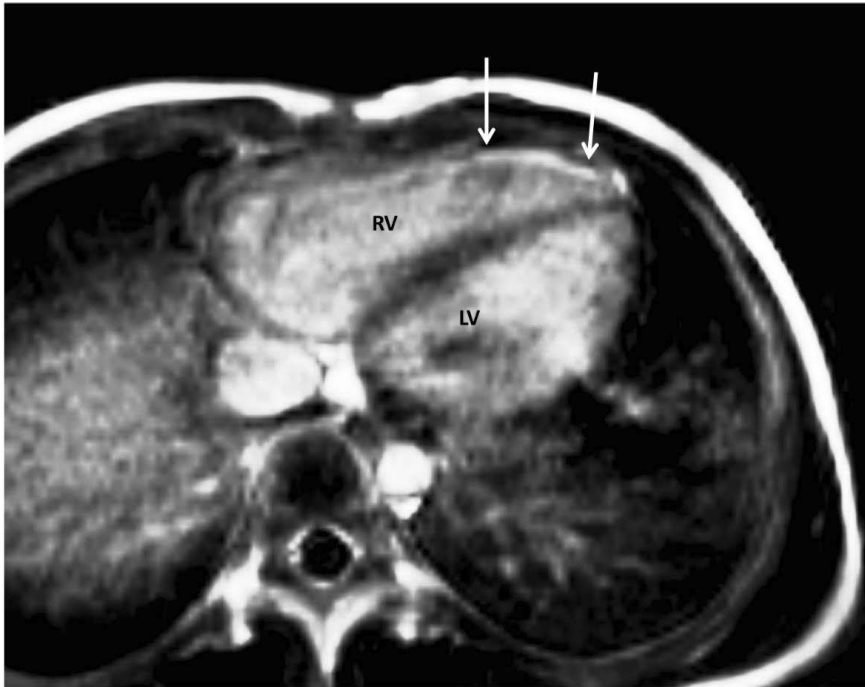
## 5.2.4 MYOCARDIAL FIBROSIS

### 5.2.4.1 Late gadolinium enhancement imaging technique

LGE detected with MRI after this contrast agent is recognized as a marker of fibrotic scars or otherwise abnormal myocardium. In study II, LGE was used to study myocardial fibrosis. Typical LGE findings are shown in Figure 13.



**Figure 13** Late gadolinium enhancements finding (white arrows) in the anterior wall of the right ventricle. Modified from Ylitalo et al., Int J Cardiol Heart Vessel 2014, with permission from Cambridge University Press.

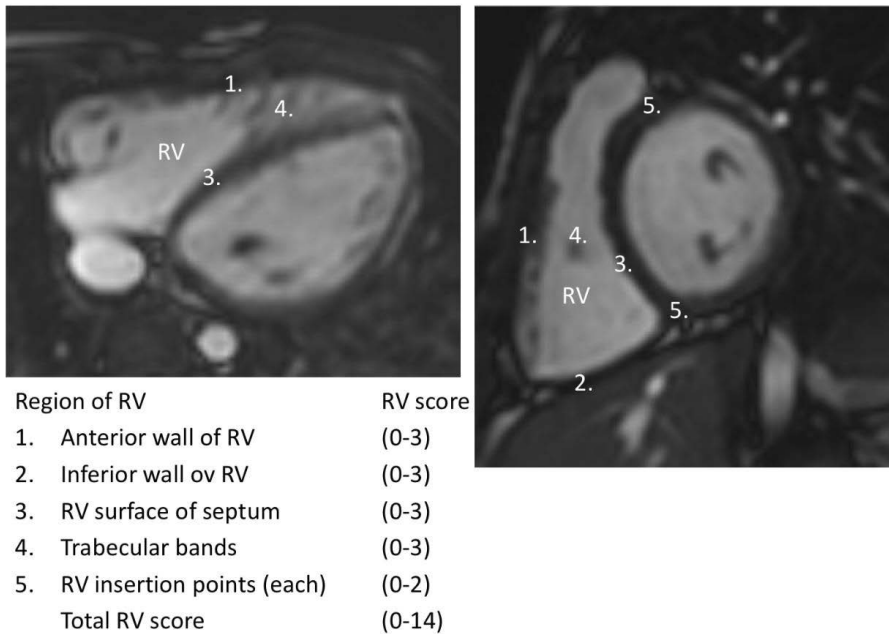


#### **5.2.4.2 LGE grading protocol**

A previously published RV LGE grading protocol that had seven RV segments (including the target locations of surgical repair) served as a basis for our grading method (109). In study II, a new grading protocol was developed as 2 surgically scarred segments (VSD patch region and the anterior wall of RVOT) of the RV were omitted to allow grading RV LGE outside the surgically intercepted myocardium.

Therefore, the following five segments were elected for the LGE grading: anterior wall of RV, inferior wall of RV, RV surface of septum, trabecular bands, and RV insertion points. Visual assessment of the late enhancement images was used and each segment was studied by grading the enhanced myocardium according to the protocol (Figure 14).

**Figure 14** Five-step segmental late gadolinium enhancement grading protocol: in the first three segments measuring right ventricular (RV) free wall and the interventricular septum, the scoring was performed as follows: 0 = no enhancements, 1 point <2 cm, 2 points = 2-3 cm, and 3 points > 3 cm in length. RV trabeculations were scored as 0 points = no enhancement, 1 point = enhancement of one trabeculation, 2 points = enhancement of 2-4 trabeculations, and 3 points = enhancement of more than 4 trabeculations. RV-LV insertion points were scored either 0 points or 1 point for absence or presence of enhancements. Modified from Ylitalo et al., Int J Cardiol Heart Vessel 2014, with permission from Cambridge University Press.



### 5.2.4.3 LGE in rTOF patients

Using our application of the grading method, LGE suggested fibrosis caused by reasons other than direct surgical manipulation. This was observed in 39 of 40 patients. LGE was not observed in any of the control subjects. LGE was frequently found in all 5 remote segments of RV and most commonly in the anterior wall in 33/40 patients (83%) followed by RV insertion points in 27/40 patients (68%). In the remaining three segments, the inferior wall was enhanced in 16/40 patients (40%), RV surface of septum in 15/40 patients (38%), and trabecular bands in 9/40 patients (23%).

RV EDV had a significant positive correlation with LGE score (Figure 15A). A PR fraction of 30% was used as a cut-off for severe PR. A higher LGE was observed in those with severe PR (n=40, P=0.008, Figure 15B). A significant

positive correlation between LGE score and post-operative follow-up time (n=40,  $r=0.44$ ,  $P=0.0045$ ) is shown in Figure 15C.

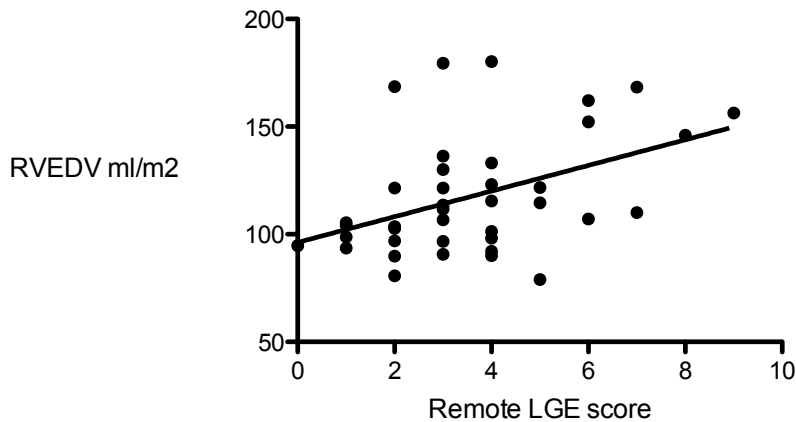
**Figure 15** A: Correlation between right ventricular end diastolic volume (RV EDV) and remote late gadolinium enhancement (LGE) score (n=40,  $r=0.44$ ,  $P=0.0045$ ).

B: Remote late gadolinium enhancement (LGE) score of patients with severe pulmonary regurgitation (PR) ( $\geq 30\%$ ) when compared with patients with PR  $< 30\%$  (n=40,  $P=0.008$ ).

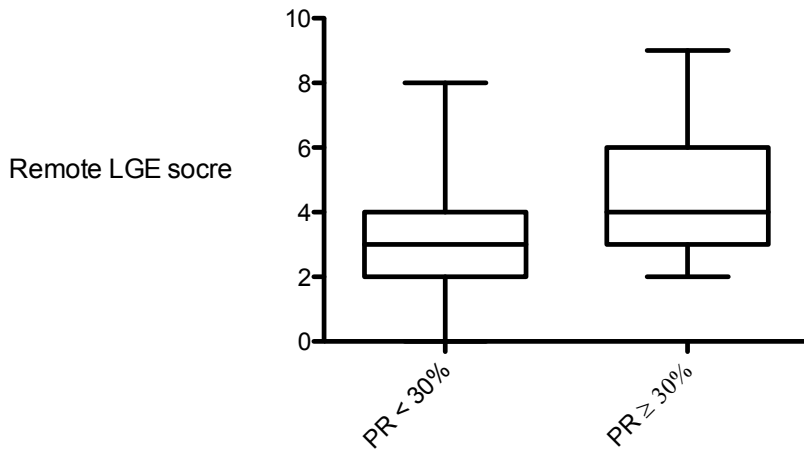
C: Correlation between post-operative follow-up time and remote LGE score (n=25,  $r=0.53$ ,  $P=0.006$ ). Only patients with  $\geq 20\%$  PR were included in this analysis.

Modified from Ylitalo et al., Int J Cardiol Heart Vessel 2014, with permission from Cambridge University Press.

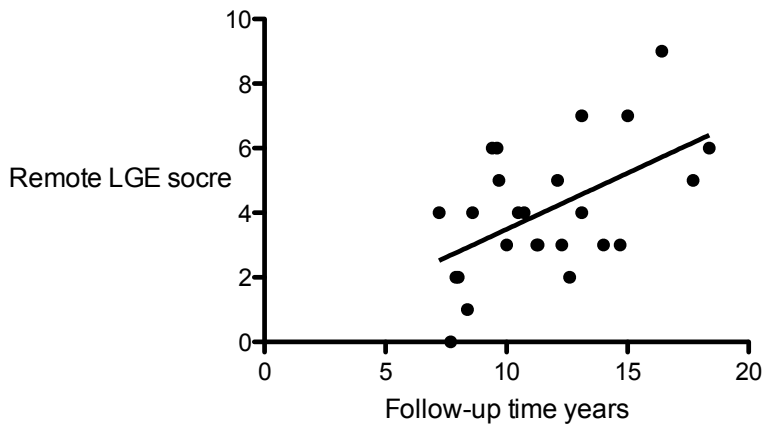
A



B



C



## 6 DISCUSSION

This thesis presents a population-based evaluation of early and late outcomes, modes of surgery, and causes of death after TOF surgery in Finland since the first primary repair in 1962. We studied the clinical state and cardiac function of paediatric and adolescent TOF patients and their healthy peers. We used novel methods for this purpose and present new findings for possible clinical use. We also propose new mechanisms behind rTOF cardiac dysfunction.

### 6.1 SURGERY OF TETRALOGY OF FALLOT IN FINLAND (STUDY I)

#### 6.1.1 EARLY AND LATE RESULTS AND CAUSES OF DEATH

##### 6.1.1.1 *Early mortality*

In this study population we reported an 85.5% survival rate. There was a total number of 82 deaths; 40 (6.7%) were early ( $\leq 30$  days after corrective surgery). During the last two decades early mortality was only 1.5% and we did not observe early deaths after the year 2000.

In a study of Hickey et al., 1181 patients operated between 1960 to 1998 had an early mortality of 10%(45). Cuypers et. al observed a 16% early mortality in patients operated between 1968 to 1980(74). Studies on early results in patients operated after 1990 report significantly lower early mortality rates (0-2%)(57, 58). Our present findings corroborate well with another Scandinavian study(42) where the authors reported a 16-year follow-up with an early mortality rate of 5.7%. These authors presented an early mortality rate of 2.1% in the 1990s and 0.6% in the 2000s in a Norwegian population. Accordingly, it seems that during the last two to three decades the early mortality has been getting close to or has even reached zero in several institutions. This is most likely due to the improved perioperative care, advanced surgical techniques, and modern intensive care.

##### 6.1.1.2 *Need for re-operation*

We observed a re-operation rate of 20.1% (n=121) during the 23-year follow-up period of our study. PVR was the most common type of re-intervention.

Lujiten et al. reported a PVR rate of 11.5% after a 15-year follow-up. A study by Park et al. stated a re-operation frequency of 31.7% with a mean follow-up

of 12.5 years(151, 152). In a study of Hickey et al., the late risk for re-operation was as high as 50% 30 years after repair and was independent of surgical era(45). Our results are comparable to these results but show lower rates of re-operation. As opposed to overall, and especially with early survival, the need for re-operations in our study remained constant over the decades and compare with the aforementioned study (45).

#### **6.1.1.3 Late survival**

We observed a late survival rate of 86% in the present patient series. Our results are consistent with a US study from 2009, where an overall survival rate of 82% in a cohort study of 1181 patients was reported. Also in this study population, the survival was higher (94%) in patients treated in the later years of TOF surgery (after 1985); early mortality was lower (2%) in these patients(45). Our present findings are consistent with a study of Linberg et al., where the authors reported a 16-year follow-up and observed an overall survival of 89% in a population of 570 patients who underwent repair between 1952 to 2008(42). Similar to our results are those from Cuypers et al., who reported a 40-year late survival rate of 86%. A study by Kirsch et al. on 277 patients operated on after 1995 reported a 10-year survival rate of 100%. Alexiou et al. reported a 20-year survival rate of 98% for 89 patients operated on between 1974 to 2000(58, 153). Accordingly, it seems that the late results are improving decade after decade. Nevertheless, we reported an increase in mortality after 40 years and therefore the late results of the 1990s and the current millennium should be later re-assessed.

#### **6.1.1.4 Causes of late mortality**

In our present patient cohort, we observed a SCD incidence of 0.12% per patient-year. SCD was the most common late cause of mortality related to cardiac reasons. Our observation of a relatively high risk of SCD is similar to what has consistently been reported in the literature. Silka et al. reported an annual incidence 0.15%(154); the overall risk of SCD has varied from 2.0% to 8.3%(59, 62, 155). In an Australian autopsy study of cardiac deaths in TOF, overall 23 decedents were analysed and 17 (74%) were classified as SCD, 4 (17%) non-cardiac, and 9% unspecified. The mean age of death in this study was 36 years.

The other two late causes of cardiac deaths in the present series were heart failure and cardiovascular death, which included all CHD-related deaths that could not be classified into SCD or heart failure. We reported a 1.8% rate of mortality due to non-cardiac causes with a diverse range of reasons, for example accidents, cancer, and suicide (Table 2).

### **6.1.2 THE METHOD OF RVOT RECONSTRUCTION**

We did not observe an increase in all-cause mortality in patients with TAP when compared to those whose pulmonary valve annulus was preserved. A Norwegian study with 16 years of follow-up similarly showed that TAP had no effect on mortality (42). Other authors have stated that late survival bears no relation to the use of TAP and have observed a better relief of RV obstruction in TAP patients. The authors also suggested the more severe morphology of these patients as a reason for this observation when compared to those with preserved pulmonary valve annulus(44). Hickey et al. made similar observations, as they did not demonstrate an association between the use of TAP and risk of late death(45).

We observed a significantly inferior event-free survival in patients if reconstruction of the RV outflow tract was performed by using TAP. The use of TAP has been reported as a significant risk factor for re-operation since the severe postoperative PR causes RV dilation, deterioration of RV function, and impairment of exercise function. The risk is especially high when the condition is accompanied by remarkable distal vessel stenosis(41). Slightly different results regarding the need of TAP were reported from a large study of 1181 patients, where both the risk of re-operation or need for PVR were not increased(45). The operative age in this study of general rTOF population was much higher (7.6 vs. 3.9 years), prior palliation was performed more often (53% vs. 25%), and the study was closed earlier (1998 vs. 2007) when compared with our study.

### **6.1.3 PRIMARY CORRECTION VS. PRIMARY PALLIATION**

Supporters of primary palliation point out that primary correction often needs aggressive RVOT resections and can possibly carry a higher risk of neonatal adverse effects and have longer postoperative recovery times(156). However, according to contemporary reports, the initial correction has no association with higher rates of early mortality when compared to a two-stage repair approach (157, 158). Higher rates of early mortality and need for re-operations have also been reported(45). Our population-based study with over 20 years of mean follow-up time revealed clearly higher mortality rates in palliated patients when compared with primary correction. The event-free survival was also inferior in this patient group. Accordingly, the initial morphology of the palliated patients was likely more complex and these patients were more often infants when a Blalock-Taussig type shunt was placed. During the current millennium, our approach of choice has been primary repair also in the youngest patients from a weight of 4 kg upwards.

## **6.2 CARDIOVASCULAR MAGNETIC RESONANCE IMAGING OF TOF PATIENTS WITH PULMONARY REGURGITATION (STUDIES II-IV)**

### **6.2.1 RIGHT VENTRICULAR VOLUMES AND FUNCTION**

During the postoperative period after repair, chronic PR is known to cause profuse diastolic filling of the RV with gradual dilation (81, 82). None of our patients reached the limit of 170 ml/m<sup>2</sup> of RVEDV, which has been suggested as one of the operative thresholds for PVR(9, 117, 120).

The clear relationship between PR and RV dilation was for the first time documented when Falliner et al. used video densitometry to quantify PR and established its relation to RV dilation(159). With CMR, the association between the degree of PR and RV size has been documented in previous studies(63, 160). Several authors have reported that the degree of PR independently predicted larger RV volume(161-163). Similar to our results (table 10), several other authors documented that the severity of PR had no effect on RV EF(63, 162-164). This finding has been contested by Lee et al., who reported a lower RV EF in patients with greater PR(165).

### **6.2.2 LEFT VENTRICULAR PRELOADING, VOLUMES, AND FUNCTION**

In study III we observed smaller LV end diastolic and stroke volumes in rTOF due to abnormal LV filling. The left atrial maximum volume, cyclic volume change, and conduit volume were smaller when compared to healthy controls. After repair necessitating TAP, profuse diastolic filling and RV dilation occur during follow-up due to PR (81, 82). These patients often present normal RV and LV functions (EFs) when they are evaluated by 2D ultrasound. However, the underlying disturbed postoperative pathophysiology and defective contractile reserve of the LV can be demonstrated with elaborate exercise-based examinations (166). Therefore, in the late survivors of TOF population, as many as 20% have developed concurrent LV dysfunction. It has even been suggested that this proportion could be as high as 70% with severe RV dilation. A progressive decline of LV function is a worrisome observation and an essential co-factor of patient deterioration that requires attention to improve late outcomes of TOF patients (71, 167).

We conclude that left atrial function is impaired in our TOF patients despite successful surgical repair and approximately 12 years of recovery. The mechanism behind likely derives from severe PR reducing transpulmonary flow and left atrial filling and LV preload volume. We suggest that this leads to impediment of ventricular interaction, LV function and LV reserves.



### 6.2.3 MYOCARDIAL CINETICS

#### 6.2.3.1 CMR Feature Tracking

CMR-FT is an emerging technique in assessing biventricular function with strain in rTOF patients. It offers several advantages when compared to MRI tagging, which is considered the gold standard method of measuring myocardial motion(101). CMR-FT is much less time consuming, does not require additional imaging sequences, and has better temporal resolution(101) when compared with myocardial tagging.

We observed increased longitudinal strain in pediatric TOF patients with severe pulmonary regurgitation. In previous studies, LV longitudinal, circumferential, and radial strains were reduced when compared to healthy controls (168-170). Similar to our findings, Berganza et al. used 2D CMR-FT and observed elevated RV circumferential strains and similar RV longitudinal strains of rTOF patients when compared to control subjects. Parallel to our study, their LV longitudinal strain was similar between patients and controls (171). We found no analysis of PR and its relation to CMR-FT findings in the recent literature, which is probably due to the novelty of the CMR-FT method.

#### 6.2.3.2 Segmental strain analysis

RVOT and the muscular surroundings of the VSD are affected during corrective surgery, regardless of the surgical method. Since superficial circumferential muscle fibres lie in parallel to these areas of manipulation, they are more likely to be injured than longitudinal fibres found especially in the free wall of the RV. It is thus possible that the apical part of the chamber left untouched during surgery could compensate for the reduced strain observed within regions subjected to injury. Our observation of increased RV apical circumferential strain in TOF patients further suggests that the deformation process serves as a compensatory mechanism. Anwar et al. reported diminished longitudinal strain of the RVOT after TAP when compared to pulmonary stenosis patients who were treated by balloon valvuloplasty(172). The authors proposed that the non-contractile TAP disturbing the RVOT contractions could explain this difference. Study IV revealed lower RV and LV EFs, which is consistent with this previous finding.

The timing of both circumferential and longitudinal RV peak systolic strain was delayed in TOF patients. We suspect that this finding derives from right bundle branch block commonly observed after TOF repair. We also reported a faster return of LV longitudinal diastolic strain to baseline in patients with TOF than in healthy subjects. LV preload and stroke volume are decreased in TOF patients due to decreased transpulmonary flow induced by PR as reported in study III. It is possible that the diastolic phase of our patients was affected

by the smaller stroke volume and therefore the ventricle reached EDV faster than in control subjects.

#### **6.2.4 MYOCARDIAL FIBROSIS**

##### **6.2.4.1 LGE in rTOF patients**

We observed LGE caused by reasons other than surgery in 39 of 40 TOF patients. LGE was not found in any of the control subjects. Severity of PR, the length of the post-operative time and RVEDV correlated positively to the LGE score. We conclude that RV myocardial LGE in remote areas of RV can be demonstrated already in young postoperative patients. Several authors have reported RV LGE as a marker of fibrosis in adult rTOF patients especially in RVOT, VSD patch region, and RV anterior wall (109, 173-175). Interestingly, LV LGE has been found in adult rTOF patients and this may be associated with adverse clinical outcomes(109, 175, 176). Similar to the findings published by Wald et al., we did not observe LV LGE among the present cohort of young rTOF patients.

Chronic PR is likely important in the process, but other non-specific contributors, such as prolonged pre-operative cyanosis and perioperative or post-operative ischemic side effects, may be involved. Importantly, the LGE score had a positive correlation with the length of postoperative follow-up time ( $r=0.53$ ,  $P=0.006$ ; Figure 11C), suggesting the deleterious effect of long-lasting PR to the myocardium. A recent report has suggested that LGE in certain locations of myocardium predict SCD in dilated cardiomyopathy. Accordingly, these patients may benefit from an implantable cardioverter defibrillator. This further addresses the importance of LGE in the follow-up of adults with TOF(177).

### **6.3 FUTURE PERSPECTIVES**

Due to the excellent early and late results of surgery of TOF, the population of children, adolescents, and especially adults with TOF is increasing. A new population-based follow-up study after 10 to 15 years would extend the follow-up time and give deeper insight in the changes of late prognosis after TOF surgery. In particular, these studies would elucidate the long-term results of patients repaired during the modern surgical era from the 1990s to the present. The oldest TOF patients are over 60 years and the course of the postoperative phase of TOF in the elderly remains to be studied as well(178). The Research Registry of Paediatric Cardiac Surgery and Finnish National Birth Registry would serve as an excellent base for a future study to assess

pregnancy outcomes of TOF and other CHD patients in a population-based setting.

Although the postoperative course and the deleterious effect of PR are well established, many questions remain unanswered. PVR is often needed during adolescence after repair of TOF. The long-term viability of the implant valves is compromised and repetitious procedures are sometimes needed. Although such procedures are routine, risks are nevertheless involved. The correct timing of the PVR is also unresolved. Subjective symptoms and exercise capacity are not informative for timing of the first RVOT reconstructive re-operation, which makes these decisions more difficult (8). PVR should probably be performed before significant RV dilation. However, despite allowing favourable remodelling of the RV, no data has accumulated regarding whether PVR would improve survival.

Big data is a term for very large and complex data sets beyond the calculation capacities of traditional data processing applications. Healthcare has benefited from big data analytics as it has provided for example clinical risk intervention and predictive analysis and broad patient- and organizational-level reporting of patient data(179). In the present study, large data sets of function, volume, kinetics, and myocardial structure of the RV, LV, and atria were collected. Combined with advanced data analytics and algorithms, new decision-making tools will likely emerge in TOF diagnostics. This may assist clinicians to effectively analyse large amounts of diverse patient information and could possibly improve decision making in daily practice.

As a last perspective for the future, our patient cohort should be invited for a re-visit and repeat the study protocol of our initial study. This approach would provide insight in progression in postoperative TOF over time.

## 7 CONCLUSIONS

1. Primary repair of tetralogy of Fallot (TOF) reduces mortality and provides longer freedom from re-operation when compared to two-stage repair. Transannular patching had no effect on late mortality but carried a higher risk of redo procedures. Event-free survival of patients has significantly shortened from the 1970s to 2000s, since re-interventions were performed progressively earlier. This is probably due to improved diagnostic tools, more frequent polyclinical follow-up, and more active surgical treatment protocols.
2. RV late gadolinium enhancement (LGE) is present in children after repair of TOF and also takes place outside surgically injured areas. The amount of LGE correlates with the severity of PR and RV dilation.
3. Transpulmonary flow of patients with TOF is affected by an abundant PR leading to impediment of left atrial filling and defective LV preload volume. Our observation may be an important additional mechanism that disturbs ventricular interaction and contributes to late-onset dysfunction of the LV.
4. Severe PR relates to enhanced longitudinal strain when compared to patients with milder regurgitation or to control subjects. TOF patients have a stronger gradual increase of RV circumferential strain from base to apex.

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